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1. Your reference — **4-32610P2/HO 61**

2. Patent application number
(The Patent Office will fill in this part) — 0220955.9 — 10 SEP 2002

3. Full name, address and postcode of the or of each applicant
(underline all surnames)

NOVARTIS AG
LICHTSTRASSE 35
4056 BASEL
SWITZERLAND

Patent ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — **SWITZERLAND**

6509648 9004

4. Title of invention — **Organic Compounds**

5. Name of your agent *(If you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent
(including the postcode)

B.A. YORKE & CO.
CHARTERED PATENT AGENTS
COOMB HOUSE, 7 ST. JOHN'S ROAD
ISLEWORTH
MIDDLESEX TW7 6NH

Patents ADP number *(if you know it)* — **1800001**

6. If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing (day/month/year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day/month/year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

c) any named applicant is a corporate body.

(see note (d))

Yes

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9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	47 ✓
Claim(s)	6 ✓
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	ONE ✓
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature B. A. Yorke & Co Date

B.A. Yorke & Co. 10 September 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs. E. Cheetham
020 8560 5847

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Notes

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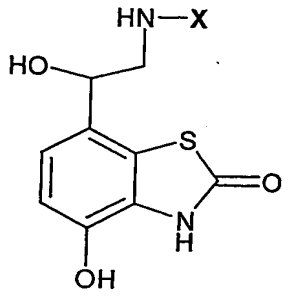
ORGANIC COMPOUNDS

This invention relates to organic compounds, their preparation and use as pharmaceuticals.

In one aspect, the present invention provides compounds of formula I



I

in free or salt or solvate form, wherein

X is $-R^1-Ar-R^2$ or $-R^a-Y$;

Ar denotes a phenylene group optionally substituted by halo, hydroxy, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy, C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl, phenyl, C_1-C_{10}-alkyl substituted by phenyl, C_1-C_{10}-alkoxy substituted by phenyl, C_1-C_{10}-alkyl-substituted phenyl or by C_1-C_{10}-alkoxy-substituted phenyl;

R^1 and R^2 are attached to adjacent carbon atoms in Ar, and
either R^1 is C_1-C_{10}-alkylene and R^2 is hydrogen, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy or halogen
or R^1 and R^2 together with the carbon atoms in Ar to which they are attached denote a 5-, 6- or 7-membered cycloaliphatic ring;

R^a is a bond or C_1-C_{10}-alkylene optionally substituted by hydroxy, C_1-C_{10}-alkoxy, C_6-C_{10}-aryl or C_7-C_{14}-aralkyl; and

Y is C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy, C_2-C_{10}-alkenyl or C_2-C_{10}-alkynyl optionally substituted by halo, cyano, hydroxy, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy or halo-C_1-C_{10}-alkyl; C_3-C_{10}-cycloalkyl optionally fused to one or more benzene rings and optionally substituted by C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy, C_3-C_{10}-cycloalkyl, C_7-C_{14}-aralkyl, C_7-C_{14}-

aralkyloxy or C_6-C_{10}-aryl optionally substituted by halo, hydroxy, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy or halo-C_1-C_{10}-alkyl;

C_6-C_{10}-aryl optionally substituted by halo, hydroxy, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy, C_1-C_{10}-haloalkyl, phenoxy, C_1-C_{10}-alkylthio, C_6-C_{10}-aryl, 4- to 10- membered heterocyclic ring having at least one ring nitrogen, oxygen or sulphur atom, or by NR^bR^c where R^b and R^c are each independently C_1-C_{10}-alkyl optionally substituted by hydroxy, C_1-C_{10}-alkoxy or phenyl or R^b may additionally be hydrogen;

phenoxy optionally substituted by C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy or by phenyl optionally substituted by C_1-C_{10}-alkyl or C_1-C_{10}-alkoxy;

a 4- to 10-membered heterocyclic ring having at least one ring nitrogen, oxygen or sulphur atom, said heterocyclic ring being optionally substituted by halo, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy, halo-C_1-C_{10}-alkyl, C_6-C_{10}-aryl, C_7-C_{14}-aralkyl, C_7-C_{14}-aralkyloxy, C_1-C_{10}-alkoxycarbonyl or a 4- to 10-membered heterocyclyl-C_1-C_{10}-alkyl;

$-NR^dR^e$ where R^d is hydrogen or C_1-C_{10}-alkyl and R^e is C_1-C_{10}-alkyl optionally substituted by hydroxy, or R^e is C_6-C_{10}-aryl optionally substituted by halo, or R^e is a 4- to 10-membered heterocyclic ring having at least one ring nitrogen, oxygen or sulphur atom which ring is optionally substituted by phenyl or halo-substituted phenyl or R^e is C_6-C_{10}-arylsulfonyl optionally substituted by C_1-C_{10}-alkylamino or di(C_1-C_{10}-alkyl)amino;

$-SR^f$ where R^f is C_6-C_{10}-aryl or C_7-C_{14}-aralkyl optionally substituted by halo, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy or C_1-C_{10}-haloalkyl; or

$-CONHR^g$ where R^g is C_1-C_{10}-alkyl, C_3-C_{10}-cycloalkyl or C_6-C_{10}-aryl.

"Halo" or "halogen" as used herein denotes a element belonging to group 17 (formerly group VII) of the Periodic Table of Elements, which may be, for example, fluorine, chlorine, bromine or iodine. Preferably halo or halogen is fluorine or chlorine.

"C_1-C_{10}-alkyl" as used herein denotes straight chain or branched alkyl that contains one to ten carbon atoms, which may be, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl,

isobutyl, sec-butyl, tert-butyl, straight or branched pentyl, straight or branched hexyl, straight or branched heptyl, straight or branched octyl, straight or branched nonyl, or straight or branched decyl. Preferably, C_1-C_{10}-alkyl is C_1-C_4-alkyl.

"C_1-C_{10}-alkylene" as used herein denotes a straight chain or branched alkylene that contains one to ten carbon atoms, for example, methylene, ethylene, trimethylene, methylethylene, tetramethylene, -$CH(CH_3)CH_2CH_2$-, -$CH_2CH(CH_3)CH_2$-, straight or branched pentylene, straight or branched hexylene, straight or branched heptylene, straight or branched octylene, straight or branched nonylene, or straight or branched decylene. Preferably C_1-C_{10}-alkylene is C_1-C_4 alkylene, especially ethylene or methylethylene.

"C_2-C_{10}-alkenyl" as used herein denotes straight chain or branched hydrocarbon chains that contain two to ten carbon atoms and one or more carbon-carbon double bonds, for example, ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, sec-butenyl, tert-butenyl, straight or branched pentenyl, straight or branched hexenyl, straight or branched heptenyl, straight or branched octenyl, straight or branched nonenyl, or straight or branched decenyl. Preferably "C_2-C_{10}-alkenyl" is "C_2-C_4-alkenyl".

"C_2-C_{10}-alkynyl" as used herein denotes straight chain or branched hydrocarbon chains that contain two to ten carbon atoms and one or more carbon-carbon triple bonds, for example, ethynyl, propynyl, isopropynyl, butynyl, isobutynyl, sec-butynyl, tert-butynyl, straight or branched pentynyl, straight or branched hexynyl, straight or branched heptynyl, straight or branched octynyl, straight or branched nonynyl, or straight or branched decynyl. Preferably "C_2-C_{10}-alkynyl" is "C_2-C_4-alkynyl".

"C_3-C_{10}-cycloalkyl" as used herein denotes cycloalkyl having 3 to 10 ring carbon atoms, for example a monocyclic group such as a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl or cyclodecyl, any of which can be substituted by one or more, usually one or two, C_1-C_4-alkyl groups, or a bicyclic group such as bicycloheptyl or bicyclooctyl. Preferably C_3-C_{10}-cycloalkyl is C_3-C_6-cycloalkyl, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

"C_1-C_{10}-haloalkyl" as used herein denotes C_1-C_{10}-alkyl as hereinbefore defined substituted by one or more halogen atoms, preferably one, two or three halogen atoms.

"C_1-C_{10}-alkylamino" and "di(C_1-C_{10}-alkyl)amino" as used herein denote amino substituted respectively by one or two C_1-C_{10}-alkyl groups as hereinbefore defined, which may be the same or different. Preferably C_1-C_{10}-alkylamino and di(C_1-C_{10}-alkyl)amino are respectively C_1-C_4-alkylamino and di(C_1-C_4-alkyl)amino.

"C_1-C_{10}-alkylthio" as used herein denotes straight chain or branched C_1-C_{10}-alkylthio, which may be, for example, methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, isobutylthio, sec-butylthio, tert-butylthio, straight or branched pentylthio, straight or branched hexylthio, straight or branched heptylthio, straight or branched octylthio, straight or branched nonylthio, or straight or branched decylthio. Preferably, C_1-C_{10}-alkylthio is C_1-C_4-alkylthio.

"C_1-C_{10}-alkoxy" as used herein denotes straight chain or branched alkoxy that contains one to ten carbon atoms which may be, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, straight or branched pentoxy, straight or branched hexyloxy, straight or branched heptyloxy, straight or branched octyloxy, straight or branched nonyloxy, or straight or branched decyloxy. Preferably, C_1-C_{10}-alkoxy is C_1-C_4-alkoxy.

"C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl" as used herein denotes C_1-C_{10}-alkyl as hereinbefore defined substituted by C_1-C_{10}-alkoxy. Preferably, C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl is C_1-C_4-alkoxy-C_1-C_4-alkyl.

"C_1-C_{10}-alkoxycarbonyl" as used herein denotes C_1-C_{10}-alkoxy as hereinbefore defined linked through an oxygen atom thereof to a carbonyl group.

"C_6-C_{10}-aryl" as used herein denotes a monovalent carbocyclic aromatic group that contains 6 to 10 carbon atoms and which may be, for example, a monocyclic group such as phenyl or a bicyclic group such as naphthyl. Preferably C_6-C_{10}-aryl is C_6-C_8-aryl, especially phenyl. "C_6-C_{10}-arylsulfonyl" as used herein denotes C_6-C_{10}-aryl as hereinbefore defined linked through a carbon atom thereof to a sulfonyl group. Preferably C_6-C_{10}-arylsulfonyl is C_6-C_8-arylsulfonyl.

"C_7-C_{14}-aralkyl" as used herein denotes alkyl, for example C_1-C_4-alkyl as hereinbefore defined, substituted by aryl, for example C_6-C_{10}-aryl as hereinbefore defined. Preferably, C_7-C_{14}-aralkyl is C_7-C_{10}-aralkyl such as phenyl-C_1-C_4-alkyl, particularly benzyl or 2-phenylethyl.

"C_7-C_{14}-aralkyloxy" as used herein denotes alkoxy, for example C_1-C_4-alkoxy as hereinbefore defined, substituted by aryl, for example C_6-C_{10}-aryl. Preferably, C_7-C_{14}-aralkyloxy is C_7-C_{10}-aralkyloxy such as phenyl-C_1-C_4-alkoxy, particularly benzyloxy or 2-phenylethoxy.

Ar as used herein may be, for example, phenylene which is unsubstituted or substituted by one or more substituents selected from halogen, hydroxy, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy, C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl, phenyl, or C_1-C_{10}-alkyl substituted by phenyl, C_1-C_{10}-alkoxy substituted by phenyl, C_1-C_{10}-alkyl-substituted phenyl and C_1-C_{10}-alkoxy-substituted phenyl. Preferably Ar is phenylene which is unsubstituted or substituted by one or two substituents selected from halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, or C_1-C_4-alkoxy substituted by phenyl. Preferably one substituent in Ar is para to R^1 and optional second and third substituents in Ar are meta to R^1.

"4- to 10-membered heterocyclic ring having at least one ring nitrogen, oxygen or sulphur atom" as used herein may be, for example, pyrrole, pyrrolidine, pyrazole, imidazole, triazole, tetrazole, thiadiazole, oxazole, isoxazole, thiophene, thiazole, isothiazole, oxadiazole, pyridine, pyrazine, pyridazine, pyrimidine, piperidine, piperazine, triazine, oxazine, morpholino, quinoline, isoquinoline, naphthyridine, indane or indene. Preferred heterocyclic rings include thiazole, pyrrolidine, piperidine, azacycloheptane and isoxazole.

"4 to 10-membered heterocyclyl-C_1-C_{10}-alkyl" denotes alkyl, for example C_1-C_{10}-alkyl as hereinbefore defined, substituted by a 4- to 10-membered heterocyclic ring as hereinbefore defined. Preferably, 4- to 10-membered heterocyclyl-C_1-C_{10}-alkyl is C_1-C_4-alkyl substituted by a 4- to 8-membered heterocyclic ring having at least one ring nitrogen, oxygen or sulphur atom.

"Optionally substituted" as used herein means the group referred to can be substituted at one or more positions by any one or any combination of the radicals listed thereafter.
R^1 and R^2 together with the carbon atoms to which they are attached as a cycloaliphatic ring may be, for example, a cyclopentane ring, optionally substituted by one or two C_1-C_4-alkyl groups, a cyclohexane ring, optionally substituted by one or two C_1-C_4-alkyl groups, or a cycloheptane ring, preferably a cyclopentane ring.

Throughout this specification and in the claims that follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be

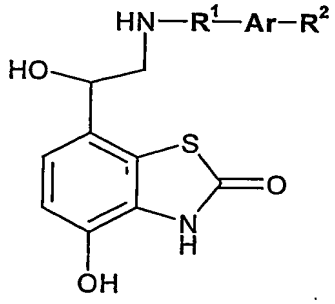
understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

Preferred compounds of formula I in free or salt or solvate form include those wherein
X is $-R^1-Ar-R^2$ or $-R^a-Y$;
Ar denotes a phenylene group optionally substituted by halo, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy or by C_1-C_{10}-alkoxy substituted by phenyl;
R^1 and R^2 are attached to adjacent carbon atoms in Ar, and
either R^1 is C_1-C_{10}-alkylene and R^2 is hydrogen,
or R^1 and R^2 together with the carbon atoms in Ar to which they are attached denote a 5-, 6- or 7-membered cycloaliphatic ring;
R^a is a bond or C_1-C_{10}-alkylene optionally substituted by hydroxy, C_6-C_{10}-aryl or C_7-C_{14}-aralkyl; and
Y is C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy or C_2-C_{10}-alkynyl; C_3-C_{10}-cycloalkyl optionally fused to one or more benzene rings and optionally substituted by C_1-C_{10}-alkyl, C_3-C_{10}-cycloalkyl, C_7-C_{14}-aralkyl, C_7-C_{14}-aralkyloxy or C_6-C_{10}-aryl; C_6-C_{10}-aryl optionally substituted by halo, hydroxy, C_1-C_{10}-alkyl, phenoxy, C_1-C_{10}-alkylthio, C_6-C_{10}-aryl, a 4- to 10-membered heterocyclic ring having at least one ring nitrogen atom, or by NR^bR^c where R^b and R^c are each independently C_1-C_{10}-alkyl optionally substituted by hydroxy or phenyl or R^b may additionally be hydrogen; phenoxy optionally substituted by C_1-C_{10}-alkoxy; a 4- to 10-membered heterocyclic ring having at least one ring nitrogen or oxygen atom, said heterocyclic ring being optionally substituted by C_1-C_{10}-alkyl, C_6-C_{10}-aryl, C_7-C_{14}-aralkyl, C_1-C_{10}-alkoxycarbonyl or by a 4- to 10-membered heterocyclyl-C_1-C_{10}-alkyl; $-NR^dR^e$ where R^d is hydrogen or C_1-C_{10}-alkyl and R^e is C_1-C_{10}-alkyl, or R^e is a 4- to 10-membered heterocyclic ring having at least one ring nitrogen or oxygen atom which ring is optionally substituted by halo-substituted phenyl or R^e is C_6-C_{10}-arylsulfonyl optionally substituted by di(C_1-C_{10}-alkyl)amino; $-SR^f$ where R^f is C_6-C_{10}-aryl or C_7-C_{14}-aralkyl optionally substituted by halo or C_1-C_{10}-haloalkyl; or $-CONHR^g$ where R^g is C_3-C_{10}-cycloalkyl or C_6-C_{10}-aryl.

Especially preferred compounds of formula I in free or salt or solvate form include those wherein
X is $-R^1-Ar-R^2$ or $-R^a-Y$;
Ar denotes a phenylene group optionally substituted by halo, C_1-C_4-alkyl, C_1-C_4-alkoxy or by C_1-C_4-alkoxy substituted by phenyl;
R^1 and R^2 are attached to adjacent carbon atoms in Ar, and

either R^1 is C_1-C_4-alkylene and R^2 is hydrogen,
or R^1 and R^2 together with the carbon atoms in Ar to which they are attached denote a 5-, 6- or 7-membered cycloaliphatic ring, especially a 5-membered cycloaliphatic ring;
R^a is a bond or C_1-C_4-alkylene optionally substituted by hydroxy, C_6-C_8-aryl or C_7-C_{10}-aralkyl; and
Y is C_1-C_4-alkyl, C_1-C_4-alkoxy or C_2-C_4-alkynyl; C_3-C_6-cycloalkyl optionally fused to one or more benzene rings and optionally substituted by C_1-C_4-alkyl, C_3-C_6-cycloalkyl, C_7-C_{10}-aralkyl, C_7-C_{10}-aralkyloxy or C_6-C_8-aryl; C_6-C_8-aryl optionally substituted by halo, hydroxy, C_1-C_4-alkyl, phenoxy, C_1-C_4-alkylthio, C_6-C_8-aryl, a 4- to 8-membered heterocyclic ring having at least one ring nitrogen atom, or by NR^bR^c where R^b and R^c are each independently C_1-C_4-alkyl optionally substituted by hydroxy or phenyl or R^b may additionally be hydrogen; phenoxy optionally substituted by C_1-C_4-alkoxy; a 4- to 8-membered heterocyclic ring having at least one ring nitrogen or oxygen atom, said heterocyclic ring being optionally substituted by C_1-C_4-alkyl, C_6-C_8-aryl, C_7-C_{10}-aralkyl, C_1-C_4-alkoxycarbonyl or by a 4- to 8-membered heterocyclyl-C_1-C_4-alkyl; $-NR^dR^e$ where R^d is hydrogen or C_1-C_4-alkyl and R^e is C_1-C_4-alkyl, or R^e is a 4- to 8-membered heterocyclic ring having at least one ring nitrogen or sulphur atom which ring is optionally substituted by halo-substituted phenyl or R^e is C_6-C_8-arylsulfonyl optionally substituted by di(C_1-C_4-alkyl)amino; $-SR^f$ where R^f is C_6-C_8-aryl or C_7-C_{10}-aralkyl optionally substituted by halo or C_1-C_4-haloalkyl; or $-CONHR^g$ where R^g is C_3-C_6-cycloalkyl or C_6-C_8-aryl.

Especially preferred compounds of formula I in free or salt or solvate form also include those of formula II

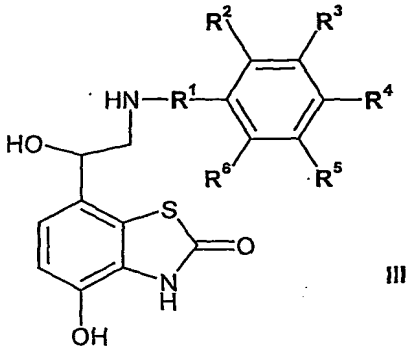


II

in free or salt or solvate form, where
Ar denotes a phenylene group optionally substituted by one or more substituents selected from halogen, C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, or C_1-C_8-alkoxy substituted by phenyl, C_1-C_8-alkyl-substituted phenyl or by C_1-C_8-alkoxy-substituted phenyl,
R^1 and R^2 are attached to adjacent carbon atoms in Ar, and

either R^1 is C_1-C_8-alkylene and R^2 is hydrogen, C_1-C_8-alkyl, C_1-C_8-alkoxy or halogen or R^1 and R^2 together with the carbon atoms in Ar to which they are attached denote a 5-, 6- or 7-membered cycloaliphatic ring.

Further preferred compounds of formula I in free or salt or solvate form include those of formula III



III

in free or salt or solvate form, where R^1 is C_2-C_4-alkylene and R^2 is hydrogen, or R^1 and R^2 together with the carbon atoms to which they are attached on the indicated benzene ring denote a 5-membered cycloaliphatic ring, R^3 and R^6 are each hydrogen, R^4 is hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy or C_1-C_4-alkoxy substituted by phenyl and R^5 is hydrogen or C_1-C_4-alkyl. Especially preferred compounds of formula I in free or salt or solvate form include those of formula II where R^1 is C_2-C_3-alkylene, R^2, R^3, R^5 and R^6 are each hydrogen, and R^4 is C_1-C_4-alkyl, C_1-C_4-alkoxy or C_1-C_4-alkoxy substituted by phenyl, and those where R^1 and R^2 together with the carbon atoms to which they are attached on the indicated benzene ring denote a cyclopentyl group fused to the benzene ring, R^3 and R^6 are each hydrogen and R^4 and R^5 are each independently hydrogen or C_1-C_4-alkyl.

The compounds represented by formula I are capable of forming acid addition salts, particularly pharmaceutically acceptable acid addition salts. Pharmaceutically acceptable acid addition salts of the compounds of formula I include those of inorganic acids, for example, hydrohalic acids such as hydrofluoric acid, hydrochloric acid, hydrobromic acid or hydroiodic acid, nitric acid, sulfuric acid, phosphoric acid; and organic acids, for example aliphatic monocarboxylic acids such as formic acid, acetic acid, trifluoroacetic acid, propionic acid and butyric acid, aliphatic hydroxy acids such as lactic acid, citric acid, tartaric acid or malic acid, dicarboxylic acids such as maleic acid or succinic acid, aromatic carboxylic acids such as benzoic acid, p-chlorobenzoic acid, diphenylacetic acid or triphenylacetic acid, aromatic hydroxy acids such as o-hydroxybenzoic acid, p-hydroxybenzoic acid, 1-hydroxynaphthalene-2-carboxylic acid or 3-hydroxynaphthalene-2-carboxylic acid, and sulfonic acids such as

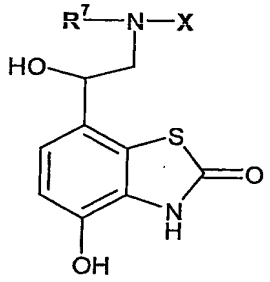
methanesulfonic acid or benzenesulfonic acid. These salts may be prepared from compounds of formula I by known salt-forming procedures.

In formula I, the carbon atom alpha to the phenolic ring carries a hydroxy group and so is asymmetric, so the compounds exist in individual optically active isomeric forms or as mixtures thereof, e.g. as racemic or diastereomeric mixtures. The invention embraces both individual optically active R and S isomers as well as mixtures, e.g. racemic or diastereomeric mixtures, thereof.

Specific especially preferred compounds of formula I are those described hereinafter in the Examples.

The present invention also provides a process for the preparation of compounds of formula I in free or salt or solvate form which comprises

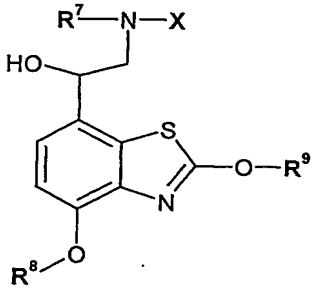
(i) either (A) reacting a compound of formula IV



IV

where X is as hereinbefore defined and R^7 denotes a protecting group, to replace R^7 by hydrogen,

or (B) reacting a compound of formula V



V

where X and R^7 are as hereinbefore defined and R^8 and R^9 each independently denote a protecting group, to convert groups R^7, R^8 and R^9 to hydrogen; and

(ii) recovering the compound of formula I in free or salt or solvate form.

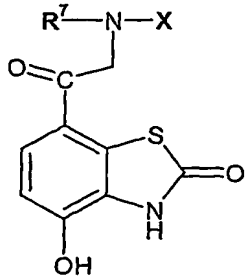
Where reference is made herein to protected functional groups or to protecting groups, the protecting groups may be chosen in accordance with the nature of the functional group, for example as described in Protective Groups in Organic Synthesis, T.W. Greene and P.G.M. Wuts, John Wiley & Sons Inc, Second Edition, 1991, which reference also describes procedures suitable for replacement of the protecting groups by hydrogen.

The protecting group R^7 may be, for example, a group chosen from known amine-protecting groups. Preferred protecting groups R^7 include araliphatic groups such as benzyl. Protecting groups R^8 and R^9 may be chosen from known phenolic hydroxy – and alcoholic hydroxy-protecting groups respectively. Preferred groups R^8 and R^9 include C_1-C_4-alkyl groups, particularly branched groups such as isopropyl and tert-butyl.

Process variant (A) may be effected, for example, using known procedures for conversion of amine-protecting groups to hydrogen or analogous procedures. For example, where R^7 is a benzyl group it may be converted to hydrogen by hydrogenolysis of the compound of formula II, e.g. with a carboxylic acid such as formic acid, preferably in the presence of a palladium catalyst. This de-protection reaction may be carried out using procedures as described hereinafter in the Examples or analogous procedures.

Process variant (B) may be effected using known procedures for conversion of hydroxy-protecting groups to hydrogen or analogous procedures. For example, where, R^8 and R^9 are alkyl groups, R^8 and R^9 may be converted to hydrogen by hydrogenolysis of the compounds of formula IV, e.g. with a carboxylic acid such as formic acid preferably in the presence of a palladium catalyst, for example as hereinbefore described for conversion of R^7 to hydrogen, or by treatment with an acid alone such as formic acid, hydrochloric acid or trifluoroacetic acid, in either case the resulting 2-hydroxybenzothiazole compound being in tautomeric equilibrium with the benzothiazol-2-one form.

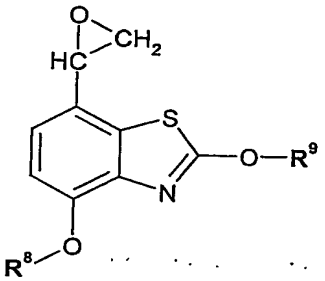
Compounds of formula IV may be prepared by reduction of a compound of formula VI



VI

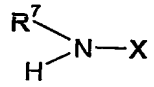
where X and R^7 are as hereinbefore defined. The reduction may be effected using known methods for reduction of ketones to alcohols, or analogous methods, including asymmetric reductions. For example, the compounds of formula VI may be reacted with $NaBH_4$ in an inert solvent such as an aliphatic alcohol. Suitable reaction temperatures are from -80° C to 100° C, conveniently from -5° C to 5° C. The reduction may be effected using known procedures or analogously as described hereinafter in the Examples.

Compounds of formula V may be prepared by reacting a compound of formula VII



VII

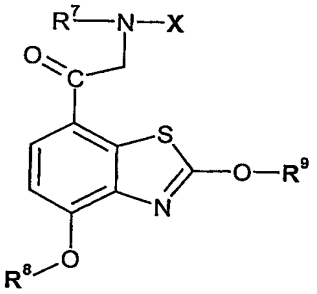
where R^8 and R^9 are as hereinbefore defined, with a compound of formula VIII



VIII

where X and R^7 are as hereinbefore defined. The reaction of compounds of formulae VII and VIII may be effected using known procedures for epoxide-amine reactions or analogous procedures. The reaction is optionally effected in an inert organic solvent, conveniently an alcohol such a n-butanol. Suitable reaction temperatures are, for example, from 0° C to solvent reflux temperature. The reaction may be effected conveniently using a procedure as described hereinafter in the Examples, or analogously.

Compounds of formula VI may be prepared by reacting a compound of formula IX

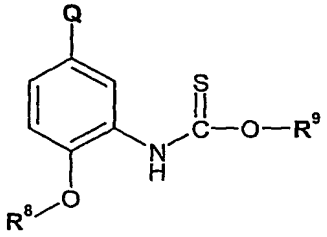


IX

where X, R^7 , R^8 and R^9 are as hereinbefore described, with concentrated hydrochloric or hydrobromic acid. The reaction is preferably carried out in an inert organic solvent such as an aliphatic alcohol.

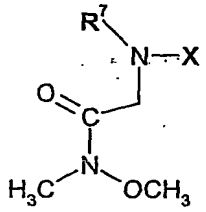
Compounds of formula VII and VIII may be prepared by known methods or analogously such as hereinafter described in the Examples.

Compounds of formula IX may be prepared by reaction of a compound of formula X



X

where Q is fluorine or chlorine and R^8 and R^9 are as hereinbefore defined, with a strong base, such as an alkyllithium, $NaNH_2$ or potassium tert-butoxide or a mixture of two or more thereof, and a compound of formula XI



XI

where X and R^7 are as hereinbefore defined. The reaction is preferably effected in an inert organic solvent, for example an ether such as tetrahydrofuran (THF). Suitable reaction temperatures may be, for example, from -80° C to 80° C. The reaction may be effected using a procedure as described hereinafter in the Examples or analogous procedures.

Compounds of formulae X and XI may be prepared using known procedures or analogously, such as described hereinafter in the Examples.

Compounds of formula I in free form may be converted into salt form, and vice versa, in a conventional manner. The compounds in free or salt form can be obtained in the form of hydrates or solvates containing a solvent used for crystallisation. Compounds of formula I can be recovered from reaction mixtures and purified in a conventional manner. Isomers, such as enantiomers, may be obtained in a conventional manner, e.g. by fractional crystallisation or asymmetric synthesis from correspondingly asymmetrically substituted, e.g. optically active, starting materials.

Compounds of formula I in free or salt or solvate form are useful as pharmaceuticals.

Accordingly the invention also provides a compound of formula I in free or salt form for use as a pharmaceutical. The compounds of formula I in free or salt form, hereinafter referred to alternatively as "agents of the invention", have good β_2-adrenoreceptor agonist activity. The β_2 agonist activity, onset of action and duration of action of the agents of the invention may be tested using the guinea pig tracheal strip in vitro assay according to the procedure of R.A. Coleman and A. T. Nials, J. Pharmacol. Methods (1989), 21(1), 71-86. The binding potency can be measured by a classical filtration binding assay according to the procedure of Current Protocols in Pharmacology (S. J. Enna et al, John Wiley & Son, Inc, 1998), or by cAMP determination in cells expressing β_2-adrenoceptor, according to the procedure of B. January et al, British J. Pharmacol. 123: 701-711 (1998). For example, the compounds of Examples 1, 3, 4 and 5 hereinbelow have Ki (β_2) values of 0.3 nM, 1.6 nM, 18.8 nM and 14.8 nM respectively.

The agents of the invention commonly have a rapid onset of action and have a prolonged stimulating action on the β_2-adrenoceptor, compounds of the Examples herein below having durations of action of the order of up to 24 hours. The compounds of Examples 4 and 5 have T(50%) times (in minutes) of 403 and 326 respectively at 10 nM concentration in the guinea pig tracheal strip assay, where T(50%) is the time for inhibition of contraction to decay to 50% of its maximum value.

Having regard to their β_2 agonist activity, the agents of the invention are suitable for use in the treatment of any condition which is prevented or alleviated by activation of the β_2-adreno-receptor. In view of their long acting β_2 agonist activity, the agents of the invention are useful in the relaxation of bronchial smooth muscle and the relief of bronchoconstriction. Relief of bronchoconstriction can be measured in models such as the in vivo plethysmography models of Chong et al, J. Pharmacol. Toxicol. Methods 1998, 39, 163-168, Hammelmann et al, Am. J. Respir. Crit. Care Med., 1997, 156, 766-775 and analogous models. The agents of the invention are therefore useful in the treatment of obstructive or inflammatory airways diseases.

In view of their long duration of action, it is possible to administer the agents of the invention once-a-day in the treatment of such diseases. In another aspect, agents of the invention commonly exhibit characteristics indicating a low incidence of side effects commonly encountered with β_2 agonists such as tachycardia, tremor and restlessness, such agents accordingly being suitable for use in on demand (rescue) treatment as well as prophylactic treatment of obstructive or inflammatory airways diseases. The incidence of side effects may be

determined, for example, as described by J. R. Fozard et al., Pulmonary Pharmacology & Therapeutics (2000) 14, 289-295.

Treatment of a disease in accordance with the invention may be symptomatic or prophylactic treatment. Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics. (For convenience this particular asthmatic condition is referred to as "wheezy-infant syndrome".)

Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, i.e. therapy for or intended to restrict or abort symptomatic attack when it occurs, for example anti-inflammatory (e.g. corticosteroid) or bronchodilatory. Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognised asthmatic syndrome, common to a substantial percentage of asthmatics and characterised by asthma attack, e.g. between the hours of about 4 to 6 am, i.e. at a time normally substantially distant form any previously administered symptomatic asthma therapy.

Other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable include acute lung injury (ALI), adult/acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary, airways or lung disease (COPD, COAD or COLD), including chronic bronchitis, or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy. The invention is also applicable to the treatment of bronchitis of whatever type or genesis including, e.g., acute, arachidic, catarrhal, croupus, chronic or phthinoid bronchitis. Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis,

including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

Having regard to their β_2 agonist activity, the agents of the invention are also useful in the treatment of a condition requiring relaxation of smooth muscle of the uterus or vascular system. They are thus useful for the prevention or alleviation of premature labour pains in pregnancy. They are also useful in the treatment of chronic and acute urticaria, psoriasis, rhinitis, allergic conjunctivitis, actinitis, hay fever, and mastocytosis.

The agents of the invention are also useful as co-therapeutic agents for use in combination with other drug substances such as anti-inflammatory, bronchodilatory or antihistamine drug substances, particularly in the treatment of obstructive or inflammatory airways diseases such as those mentioned hereinbefore, for example as potentiators of therapeutic activity of such drugs or as a means of reducing required dosaging or potential side effects of such drugs. An agent of the invention may be mixed with the other drug substance in a fixed pharmaceutical composition or it may be administered separately, before, simultaneously with or after the other drug substance.

Such anti-inflammatory drugs include steroids, in particular glucocorticosteroids such as budesonide, beclamethasone, fluticasone, ciclesonide or mometasone, LTB4 antagonists such as those described in US 5451700, LTD4 antagonists such as montelukast and zafirlukast, and PDE4 inhibitors such as Ariflo® (GlaxoSmith Kline), Roflumilast (Byk Gulden),V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering-Plough), Arofylline (Almirall Prodesfarma) and PD189659 (Parke-Davis).

Such bronchodilatory drugs include anticholinergic or antimuscarinic agents, in particular ipratropium bromide, oxitropium bromide and tiotropium bromide.

Co-therapeutic antihistamine drug substances include cetirizine hydrochloride, acetaminophen, clemastine fumarate, promethazine, loratidine, desloratidine, diphenhydramine and fexofenadine hydrochloride. Combinations of agents of the invention and steroids, beta-2 agonists, PDE4 inhibitors or LTD4 antagonists may be used, for example, in the treatment of COPD or, particularly, asthma. Combinations of agents of the invention and anticholinergic or antimuscarinic agents, PDE4 inhibitors, dopamine receptor agonists or LTB4 antagonists may be used, for example, in the treatment of asthma or, particularly, COPD.

In accordance with the foregoing, the present invention also provides a method for the treatment of an obstructive or inflammatory airways disease which comprises administering to a subject, particularly a human subject, in need thereof an effective amount a compound of formula I, or a pharmaceutically acceptable salt thereof, as hereinbefore described. In another aspect, the invention provides a compound of formula I, or a pharmaceutically acceptable salt thereof, as hereinbefore described for use in the preparation of a medicament for the treatment of an obstructive or inflammatory airways disease.

The agents of the invention may be administered by any appropriate route, e.g. orally, for example in the form of a tablet or capsule; parenterally, for example intravenously; topically to the skin, for example in the treatment of psoriasis; intranasally, for example in the treatment of hay fever; or, preferably, by inhalation, particularly in the treatment of obstructive or inflammatory airways diseases.

In a further aspect, the invention also provides a pharmaceutical composition comprising as active ingredient a compound of formula I in free form or in the form of a pharmaceutically acceptable salt or solvate thereof, optionally together with a pharmaceutically acceptable diluent or carrier therefor. Such compositions may be prepared using conventional diluents or excipients and techniques known in the galenic art. Thus oral dosage forms may include tablets and capsules. Formulations for topical administration may take the form of creams, ointments, gels or transdermal delivery systems, e.g. patches. Compositions for inhalation may comprise aerosol or other atomizable formulations.

When the composition comprises an aerosol formulation, it preferably contains, for example, a hydro-fluoro-alkane (HFA) propellant such as HFA134a or HFA227 or a mixture of these, and may contain one or more co-solvents known in the art such as ethanol (up to 20% by weight), and/or one or more surfactants such as oleic acid or sorbitan trioleate, and/or one or more bulking agents such as lactose. When the composition comprises a dry powder formulation, it preferably contains, for example, the compound of formula I having a particle diameter up to 10 microns, optionally together with a diluent or carrier, such as lactose, of the desired particle size distribution and a compound that helps to protect against product performance deterioration due to moisture. When the composition comprises a nebulised formulation, it preferably contains, for example, the compound of formula I either dissolved, or suspended, in a vehicle containing water, a co-solvent such as ethanol or propylene glycol and a stabiliser, which may be a surfactant.

The invention also includes (A) a compound of formula I as hereinbefore described in free form, or a pharmaceutically acceptable salt or solvate thereof, in inhalable form; (B) an inhalable medicament comprising such a compound in inhalable form together with a pharmaceutically acceptable carrier in inhalable form; (C) a pharmaceutical product comprising such a compound in inhalable form in association with an inhalation device; and (D) an inhalation device containing such a compound in inhalable form.

Dosages employed in practising the invention will of course vary depending, for example, on the particular condition to be treated, the effect desired and the mode of administration. In general, suitable daily dosages for administration by inhalation are of the order of from 0.1 to 5000 μg.

The invention is illustrated by the following Examples.

Certain compounds that are used to prepare compounds of the Examples that are not readily commercially available are prepared as follows:

Preparation 1: [4-(4-phenyl-butoxy)-phenyl]-acetonitrile

1-Chloro-4-phenylbutane is added to a suspension of 4-hydroxyphenylacetonitrile (1.91 g), K_2CO_3 (4.64 g) and sodium iodide (600 mg) in acetonitrile (30 ml) and refluxed for 68 hours. Filtration, evaporation followed by silica gel flash column chromatography, eluent 4:1 hexane: $CH_3CO_2CH_2CH_3$, gives the title compd. ^{1}H nmr (d_6-DMSO, 400 MHz); 7.30-7.13 (m, 7H), 6.95-6.87 (m, 2H), 3.97 (t, J=6 Hz, 2H), 3.92 (s, 2H), 2.62 (t, J=7 Hz, 2H), 1.77-1.63 (m, 4H).

Preparation 2: 2-[4-(4-phenyl-butoxy)-phenyl]-ethylamine

The title compound (395 mg) is prepared from [4-(4-phenyl-butoxy)-phenyl]-acetonitrile (500 mg) by the procedure of B. Staskun et al J. Chem Soc. (C) 1966, 531. ^{1}H nmr (d_6-DMSO, 400 MHz); 7.32-7.10 (m, 5H), 7.10-7.00 (m, 2H), 6.83-6.75 (m, 2H), 3.97-3.80 (m, 2H), 3.70-2.87 (br s, 2H), 2.73-2.45 (m, 6H), 1.77-1.60 (m, 4H).

Preparation 3: benzyl-[2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amine

The title compound (2.1 g) is prepared from 2-[4-(4-phenyl-butoxy)-phenyl]-ethylamine by the procedure of A. F. Abdel-Magid J. Org. Chem. 1996, 61, 3849. MS (ES+) 361.

Prep. 4: (benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amino)-acetic acid tert-butyl ester

Butyl bromoacetate (4.94 ml) is added to a solution of benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amine (10 g) and N,N-diisopropylethylamine (10.2 ml) in tetrahydrofuran (THF) (40 ml) at 0° C. After 18 hours at room temperature the reaction mixture is partitioned between aqueous $NaHCO_3$ and $CH_3CO_2CH_2CH_3$, followed by evaporation of the $CH_3CO_2CH_2CH_3$ layers and silica gel column chromatography, eluent 9:1 hexane:$CH_3CO_2CH_2CH_3$, to give the title compound. MS (ES+) 474.

Preparation 5: tert-butoxy-5-fluoro-phenylamine

A suspension of platinum oxide (17 g) in a solution of 1-tert-butoxy-4-fluoro-2-nitro-benzene (225 g, prepared by procedure T. F. Woiwode et al J. Org. Chem. 1998, 63, 9594.) in CH_3OH (1.5 l) is stirred under an atmosphere of hydrogen for 18 hours. Filtration through Celite and evaporation gives the title compound. ^{19}F nmr ($CDCl_3$, 376 MHz); -43.4.

Preparation 6: (benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amino)-acetic acid

A solution of (benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amino)-acetic acid tert-butyl ester (12.1 g) in CH_2Cl_2 (50 ml) and CF_3CO_2H (30 ml) is stirred for 18 hours at room temperature after which evaporation gives the title compound. MS (ES+) 418.

Preparation 7: 1-tert-butoxy-4-fluoro-2-isothiocyanato-benzene

Carbon disulphide (38.6 ml) is added to a solution of 2-tert-butoxy-5-fluoro-phenylamine (58.8 g) and triethylamine (89.5 ml) in toluene (66 ml) and the reaction mixture stirred at room temperature for 18 hours, then evaporated. Chloroform (200 ml) and triethylamine (44.9 ml) are added to the residue, which is cooled before the addition of ethyl chloroformate (30.8 ml). After 15 minutes at 0°C, the reaction mixture is washed sequentially with aqueous 3N HCl, saturated brine, saturated $NaHCO_3$ and saturated brine, then evaporated to give the title compound. ^1H nmr ($CDCl_3$, 400 MHz); 7.10-7.03 (m, 1H), 6.93-6.87 (m, 1H), 6.86-6.80 (m, 1H), 1.43 (s, 9H).

Preparation 8: 2-(benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amino)-N-methoxy-N-methyl-acetamide

1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (5.30 g) is added to a solution of (benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amino)-acetic acid (12.56 g), N,N-dimethylaminopyridine (3.38 g), N,O-dimethylhydroxylamine (8.09 g) and N-methylmorpholine (6.08 ml) in tetrahydrofuran (150 ml). After refluxing for 4 hours, the

reaction mixture is partitioned between water and $CH_3CO_2CH_2CH_3$. Evaporation of the $CH_3CO_2CH_2CH_3$ layers and silica gel column chromatography, eluent 9:1 hexane: $CH_3CO_2CH_2CH_3$, gives the title compound. MS (ES+) 461.

Preparation 9: (2-tert-butoxy-5-fluoro-phenyl)-thiocarbamic acid O-isopropyl ester

A solution of 1-tert-butoxy-4-fluoro-2-isothiocyanato-benzene (50.0 g) and triethylamine (31 ml) in isopropanol (170 ml) is refluxed for 48 hours. Evaporation of the reaction mixture followed by silica gel flash column chromatography, eluent 20:1 hexane: $CH_3CO_2CH_2CH_3$ gives the title compound. ^1H nmr ($CDCl_3$, 400 MHz); 8.60 (br s, 1H), 7.38 (br s, 1H), 7.50-6.87 (m, 1H), 6.67-6.58 (m, 1H), 5.64-5.50 (m, 1H), 1.43-1.32 (m, 6H), 1.32-1.25 (s, 9H).

Preparation 10: 2-(benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amino)-1-(4-tert-butoxy-2-isopropoxy-benzothiazol-7-yl)-ethanone

A solution of tert. butyl lithium in pentane (12.3 ml, 1.7 M) is added to a solution of (2-tert-butoxy-5-fluoro-phenyl)-thiocarbamic acid O-isopropyl ester (3.20 g) in tetrahydrofuran (10 ml) at –78° C, the solution warmed to –20° C over 1 hour then re-cooled –78° C and a solution of 2-(benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amino)-N-methoxy-N-methyl-acetamide in tetrahydrofuran (10 ml) added at –78° C. The reaction mixture is warmed to room temperature and partitioned between aqueous NH_4Cl and $CH_3CO_2CH_2CH_3$. Evaporation of the $CH_3CO_2CH_2CH_3$ layers and silica gel column chromatography, eluent 4:1 hexane: $CH_3CO_2CH_2CH_3$, gives the title compound. MS (ES+) 665.

Preparation 11: 7-[(benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amino)-acetyl]-4-hydroxy-3H-benzothiazol-2-one

A solution of 2-(benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amino)-1-(4-tert-butoxy-2-isopropoxy-benzothiazol-7-yl)-ethanone (2.49 g) in isopropanol (20 ml) and concentrated hydrobromic acid (20 ml) is heated at 50° C. After 3 hours the reaction mixture is partitioned between $CH_3CO_2CH_2CH_3$ and water, and the $CH_3CO_2CH_2CH_3$ layer washed with aqueous $NaHCO_3$ then brine. Evaporation of the $CH_3CO_2CH_2CH_3$ layers and silica gel column chromatography, eluent 4:1 hexane: $CH_3CO_2CH_2CH_3$, gives the title compd. MS (ES+) 567.

Preparation 12: 7-[2-(benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amino)-1-hydroxy-ethyl]-4-hydroxy-3H-benzothiazol-2-one

$NaBH_4$ (2.67 g) is added portion-wise to a solution of 7-[(benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amino)-acetyl]-4-hydroxy-3H-benzothiazol-2-one (0.40 g) in CH_3OH (15 ml) at

0° C. After 30 minutes the reaction mixture is partitioned between $CH_3CO_2CH_2CH_3$ and water. Evaporation of the $CH_3CO_2CH_2CH_3$ layers and silica gel column chromatography, eluent 1:1 hexane: $CH_3CO_2CH_2CH_3$, gives the title compound. MS (ES+) 569.

Preparation 13: benzyl-indan-2-ylamine

The title compound is prepared from indan-2-one by the procedure of A. F. Abdel-Magid et al J. Org. Chem. 1996, 61, 3849. MS (ES+) 224.

Preparation 14: 2-(benzyl-indan-2-yl-amino)-N-methoxy-N-methyl-acetamide

The title compound is prepared from benzyl-indan-2-ylamine by procedures analogous to those of Preparations 4, 6 and 8. MS (ES+) 326.

Prep. 15: 7-[2-(benzyl-[2-indan-2-yl]amino)-1-hydroxyethyl]-4-hydroxy-3H-benzothiazolone

The title compound is prepared from 2-(benzyl-indan-2-yl-amino)-N-methoxy-N-methyl-acetamide and (2-tert-butoxy-5-fluoro-phenyl)-thiocarbamic acid O-isopropyl ester using procedures analogous to those of Preparations 10, 11 and 12.

Preparation 16: 2-[benzyl-(5,6-diethyl-indan-2-yl)-amino]-N-methoxy-N-methyl-acetamide

The title compound is prepared from 5,6-diethyl-indan-2-ylamine (prepared by the procedure of WO 0075114) by procedures analogous to those of Prep. 3, 4, 6 and 8. MS (ES+) 382.

Preparation 17: 2-{benzyl-[(R)-2-(4-methoxy-phenyl)-1-methyl-ethyl]-amino}-N-methoxy-N-methyl-acetamide

The title compound Is prepared from (R)-2-(4-methoxy-phenyl)-1-methyl-ethylamine (R. Hett et al Tetrahedron Lett. 1997, 38, 1125.) by procedures analogous to those of Preparations 3, 4, 6 and 8. MS (ES+) 358.

Preparation 18: 2,2,2-trifluoro-N-phenethyl-acetamide

Trifluoroacetic anhydride (64.5 ml) is added dropwise to a solution of phenethylamine (52 ml) and triethylamine (58 ml) in CH_2Cl_2 at 0° C. After 18 hours at room temperature the reaction mixture is washed with aqueous citric acid, brine and aqueous $NaHCO_3$, dried with $MgSO_4$ and evaporated to give the title compound.

Preparation 19: 2,2,2-trifluoro-N-[2-(4-isobutyryl-phenyl)-ethyl]-acetamide

Isobutryl chloride (19.7 ml) is added dropwise to a mixture of 2,2,2-trifluoro-N-phenethyl-acetamide (34.2 g) and aluminium chloride (48.2 g) in CH_2Cl_2 (450 ml) at 0° C. After 18 hours at room temperature the reaction mixture is poured onto ice (2000 g), extracted 3 times with CH_2Cl_2, dried with $MgSO_4$ and evaporated to give the title compound which is used without further purification.

Preparation 20: 2,2,2-trifluoro-N-[2-(4-isobutyl-phenyl)-ethyl]-acetamide

A solution of 2,2,2-trifluoro-N-[2-(4-isobutyryl-phenyl)-ethyl]-acetamide (19.4 g) in ethanol (200 ml) and conc. hydrochloric acid (5 ml) is stirred for 23 hours under 1 atm of hydrogen over a palladium on carbon catalyst (1.9 g). Filtration, evaporation and purification by silica gel chromatography, eluting with chloroform, gives the title compound. ^{13}C nmr ($CDCl_3$, 101 MHz); 157.55, 140.90, 135.10, 130.03, 128.78, 45.40, 41.46, 34.94, 30.61, 22.72.

Preparation 21: 2-(4-isobutyl-phenyl)-ethylamine

Potassium carbonate (18.5 g) is added to a solution of 2,2,2-trifluoro-N-[2-(4-isobutyl-phenyl)-ethyl]-acetamide (12.2 g) in methanol (45 ml) and water (19 ml) at room temp. The mixture is heated at 45° C for 8 hours. Dilution with water (200 ml), extraction with dichloromethane, drying over $MgSO_4$ and evaporation gives the title compound. ^{13}C nmr ($CDCl_3$, 101 MHz); 140.10, 137.40, 129.56, 128.94, 45.45, 43.99, 40.01, 30.45, 22.79.

Preparation 22: {benzyl-[2-(4-isobutyl-phenyl)-ethyl]-amino}-acetic acid

The title compound is prepared from 2-(4-isobutyl-phenyl)-ethylamine by procedures analogous to those of Preparations 3, 4 and 6. MS (ES+) 326.

Prep. 23: 2-{benzyl-[2-(4-isobutyl-phenyl)-ethyl]-amino}-N-methoxy-N-methyl-acetamide

Isobutyl chloroformate (0.54 ml) is added to a solution of {benzyl-[2-(4-isobutyl-phenyl)-ethyl]-amino}-acetic acid (1.5 g) and Hunig's base (3.61 ml) in dichloromethane (21 ml) at 0°C. After 2 hours N,O-dimethylhydroxylamine hydrochloride (0.49 g) is added, the reaction stirred a further 30 minutes at 0°C then partitioned between aqueous $NaHCO_3$ and CH_2Cl_2, dried over $MgSO_4$, evaporated and purified by silica gel chromatography, eluting with 10% ethyl acetate in CH_2Cl_2, to give the title compound. MS (ES+) 370.

Prep. 24: 2-{benzyl-[2-(4-propyl-phenyl)-ethyl]-amino}-N-methoxy-N-methyl-acetamide

The title compound is prepared from 2,2,2-trifluoro-N-phenethyl-acetamide by procedures analogous to those of Preparations 19, 20, 21, 3, 4, 6 and 22. MS (ES+) 356 (96%), 266.

Preparation 25: N-benzyl-2-(4-bromo-phenyl)-acetamide

4-Bromophenylacetic acid (23.24 g) is dissolved in dichloromethane (400 ml). 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (20.70 g) is added followed by DMAP (0.13 g) and the reaction mixture stirred at room temperature for 10 minutes. Benzylamine (12.14 g), dissolved in dichloromethane (100 ml), is then slowly added and the reaction mixture stirred at room temperature. After 1 hour the reaction is shown to be complete by TLC. The reaction mixture is washed with 1M HCl (3 x 200 ml), water (3 x 200 ml) and brine (200 ml). The organic layer dried is over $MgSO_4$, filtered and the solvent removed in vacuo. The title compound is obtained following crystallisation from ethylacetate. MS (ES+) m/e 304 ($MH^+ - Br^{79}$) and 306 ($MH^+ - Br^{81}$).

Preparation 26: N-benzyl-2-(4-propyl-phenyl)-acetamide

1,1'-Bis(diphenylphosphino)ferrocenedichloro palladium(II) (0.39 g) is placed in a flask under an atmosphere of argon. The flask is cooled to –78° C and then propylzinc bromide (200 ml, 0.5 M in THF) is slowly added. N-Benzyl-2-(4-bromo-phenyl)-acetamide (14.48 g, 47.62 mmol), dissolved in THF (500 ml), is then slowly added and the reaction mixture stirred at room temperature. After 24 hours further propylzinc bromide (10 ml, 0.5 M in THF) is added and the reaction mixture stirred at room temperature. The reaction is shown to be complete by TLC after 24 hours and is quenched by the addition of 2M HCl (50 ml) and then 80-90% of the solvent is removed in vacuo. The residue is partitioned between ethyl acetate (250 ml) and water (250 ml). The organic layer is washed with water (250 ml) and brine (250 ml), dried over $MgSO_4$, filtered and the solvent removed in vacuo. Recrystallisation from cyclohexane gives the title compound. MS (ES+) m/e 268 (MH^+).

Preparation 27: benzyl-[2-(4-propyl-phenyl)-ethyl]-amine hydrochloride

DIBAL (47.5 ml, 1.5M in toluene) is slowly added to N-benzyl-2-(4-propyl-phenyl)-acetamide (9.50 g) in toluene (200 ml) cooled on an ice-bath. The reaction mixture is stirred at room temperature until shown to be complete by TLC. The reaction mixture is recooled on an ice-bath and quenched by the addition of water (10 ml), washed further with water (2 x 100 ml) and brine (100 ml), dried over $MgSO_4$, filtered and the solvent removed in vacuo. The residue is taken up in hexane : ethylacetate (5 :1) (100 ml) and any insoluble material is filtered off. The solvent is removed in vacuo and the residue dissolved in Et_2O. 1M HCl in Et_2O (30ml) is added and the title compound obtained by filtration. MS (ES+) m/e 254 (MH^+).

Preparation 28: 1-(4-tert.butoxy-2-isopropoxy-benzothiazol-7-yl)-2-chloro-ethanone

Tert. butyllithium (22.7 ml, 1.7 M in pentane) is added dropwise to a solution of (2-tert. butoxy-5-fluoro-phenyl)-thiocarbamic acid O-isopropyl ester (5.00 g) in THF (20 ml) at –78° C. This solution is then allowed to warm to –20° C and a dried mixture of lithium chloride (2.12 g) and copper (I) cyanide (2.24 g) in THF (50 ml) is added. After 15 minutes chloroacetyl chloride (4.36 g) is added and the reaction mixture allowed to warm to 0° C. This temperature is maintained for 1 hour and then the reaction mixture is quenched by the addition of saturated aqueous NH_4Cl (5 ml). The reaction mixture is partitioned between ethyl acetate (250 ml) and water (250 ml). The organic layer is washed with water (250 ml) and brine (250 ml), dried over $MgSO_4$, filtered and the solvent removed in vacuo. The title compd is obtained by flash column chromatography (silica, iso-hexane / ethyl acetate 10:1). MS (ES+) m/e 341 (MH^+).

Preparation 29: (R)-1-(4-tert-butoxy-2-isopropoxy-benzothiazol-7-yl)-2-chloro-ethanol

Borane-THF complex, (14.64 ml, 1M in THF) is added dropwise to a solution of (1R, 2S)-(+)-1-amino-2-indanol (0.22 g) in THF (50 ml) and the solution is stirred at room temperature for 15 minutes. A solution of 1-(4-tert.butoxy-2-isopropoxy-benzothiazol-7-yl)-2-chloro-ethanone (5.00 g) in THF (50 ml) is then added dropwise over a period of 1 hour. The reaction mixture is stirred at room temperature for a further 15 minutes and then quenched by the addition of 0.2M H_2SO_4 (5 ml). The reaction mixture is partitioned between ethyl acetate (200 ml) and 0.2M H_2SO_4 (200 ml). The organic layer is washed with water (200 ml) and brine (200 ml), dried over $MgSO_4$, filtered and the solvent removed in vacuo to give the title compound. MS (ES+) m/e 344 (MH^+).

Preparation 30: 4-tert.butoxy-2-isopropoxy-7-(R)-oxiranyl-benzothiazole

A mixture of (R)-1-(4-tert.butoxy-2-isopropoxy-benzothiazol-7-yl)-2-chloro-ethanol (4.70 g) and potassium carbonate (7.48 g) in acetone (250 ml) is refluxed for 48 hours. The reaction mixture is allowed to cool, filtered and the solvent removed in vacuo to give the title compound. MS (ES+) m/e 308 (MH^+).

Preparation 31: (R)-2-[benzyl-[2-(4-propyl-phenyl)-ethyl]-amino]-1-(4-tert-butoxy-2-isopropoxy-benzothiazol-7-yl)-ethanol

A solution of 4-tert.butoxy-2-isopropoxy-7-(R)-oxiranyl-benzothiazole (3.50 g) and benzyl-[2-(4-propyl-phenyl)-ethyl]-amine (3.03 g) in 1-butanol (25 ml) is stirred at 110° C. The reaction

is shown to be complete by TLC after 18 hours. The title compound is obtained after purification by flash column chromatography (silica, iso-hexane / ethyl acetate 10:1). MS (ES+) m/e 561 (MH^+).

Preparation 32: (S)-1-(4-tert-butoxy-2-isopropoxy-benzothiazol-7-yl)-2-chloro-ethanol

The title compd is prepared by a procedure analogous to that of Prep 29 using Borane-THF complex, (14.64 ml, 1 M in THF), (1S, 2R)-(-)-1-amino-2-indanol (0.22 g) and 1-(4-tertbutoxy-2-isopropoxy-benzothiazol-7-yl)-2-chloro-ethanone (5.00 g). MS (ES+) m/e 344 (MH^+).

Preparation 33: (5,6,7,8-Tetrahydro-naphthalen-2-yl)-acetic acid

The title compound is prepared from 6-acetyltetralin by the procedure of G. Giardina et al J. Med. Chem. 1994, 37, 3482. ^1H nmr ($CDCl_3$, 400 MHz); 7.00 (m, 3H), 3.55 (s, 2H), 2.75 (m, 4H), 1.75 (m, 4H).

Preparation 34: N-Benzyl-2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-acetamide

The title compound is prepared by a procedure analogous to that of Preparation 25 using (5,6,7,8-Tetrahydro-naphthalen-2-yl)-acetic acid. ^1H nmr ($CDCl_3$, 400 MHz); 7.30-7.15 (m, 5H), 7.05-6.90 (m, 3H), 5.70 (br s, 1H), 3.55 (s, 2H), 2.70 (m, 4H), 1.75 (m, 4H).

Preparation 35: Benzyl-[2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-ethyl]-amine hydrochloride

The title compound is prepared by a procedure analogous to that of Preparation 27 using N-Benzyl-2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-acetamide. ^1H nmr (d_6-DMSO, 400 MHz); 9.40 (br s, 2H), 7.55 (m, 2H), 7.40 (m, 3H), 7.00-6.85 (m, 3H), 4.10 (m, 2H), 3.05 (m, 2H), 2.90 (m, 2H), 2.65 (m, 4H), 1.70 (m, 4H).

Preparation 36: (R)-2-{Benzyl-[2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-ethyl]-amino}-1-(4-tert-butoxy-2-isopropoxy-benzothiazol-7-yl)-ethanol

The title compound is prepared by a procedure analogous to that of Preparation 31 using Benzyl-[2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-ethyl]-amine. ^1H nmr ($CDCl_3$, 400 MHz); 7.35-7.20 (m, 5H), 7.00-6.95 (m, 3H), 6.90-6.80 (m, 2H), 5.45 (m, 1H), 4.70 (m, 1H), 3.95 (d, 1H), 3.55 (d, 1H), 2.85 (m, 6H), 2.70 (m, 4H), 1.75 (m, 4H), 1.45 (m, 6H), 1.35 (s, 9H).

Preparation 37: 1-(3,4-Diethyl-phenyl)-ethanone

1,2-Diethylbenzene (9.24 g, 69 mmol) and acetyl chloride (5.42 g, 69 mmol) are added dropwise to $AlCl_3$ (20.63 g, 155 mmol) in nitromethane (50 ml) over 30 minutes. The reaction mixture is stirred at room temperature for 2 hours, after which 200 g of ice and 15 ml

concentrated hydrochloric acid are added. The aqueous phase is extracted with ether, and the combined organic phases extracted with 2 N HCl and saturated aqueous NaCl. The organic phase is dried over magnesium sulphate, filtered, and the solvent removed *in vacuo* to give the title compound. ^{1}H nmr ($CDCl_3$, 400 MHz); 7.75 (d, 1H), 7.70 (d of d, 1H), 7.15 (d, 1H), 2.70 (m, 4H), 2.55 (s, 3H), 1.20 (m, 6H).

Preparation 38: Benzyl-[2-(3,4-diethyl-phenyl)-ethyl]-amine hydrochloride

The title compound is prepared from 1-(3,4-Diethyl-phenyl)-ethanone using procedures analogous to those of Preparations 33, 25 and 27. ^{1}H nmr (d_6-DMSO, 400 MHz); 9.40 (br s, 2H), 7.55 (m, 2H), 7.40 (m, 3H), 7.10 (m, 1H), 7.00- (m, 2H), 4.15 (m, 2H), 3.05 (m, 2H), 2.90 (m, 2H), 2.55 (m, 4H), 1.10 (m, 6H).

Preparation 39: Benzyl-[2-(4-ethoxy-3-methoxy-phenyl)-ethyl]-amine hydrochloride

The title compound is prepared from (4-Ethoxy-3-methoxy-phenyl)-acetic acid using procedures analogous to those of Preparations 25 and 27. ^{1}H nmr (d_6-DMSO, 400 MHz); 9.40 (br s, 2H), 7.55 (m, 2H), 7.40 (m, 3H), 6.85 (m, 2H), 6.70 (m, 1H), 4.15 (m, 2H), 3.95 (q, 2H), 3.75 (s, 3H), 3.10 (m, 2H), 2.90 (m, 2H), 1.30 (t, 4H).

Preparation 40: (R)-2-{Benzyl-[2-(4-ethoxy-3-methoxy-phenyl)-ethyl]-amino}-1-(4-tert-butoxy-2-isopropoxy-benzothiazol-7-yl)-ethanol

The title compound is prepared by a procedure analogous to that of Preparation 31 using Benzyl-[2-(4-ethoxy-3-methoxy-phenyl)-ethyl]-amine. ^{1}H nmr ($CDCl_3$, 400 MHz); 7.35-7.20 (m, 5H), 6.95 (m, 2H), 6.80 (d, 1H), 6.65 (m, 2H), 5.45 (m, 1H), 4.70 (m, 1H), 4.05 (q, 2H), 3.95 (d, 1H), 3.80 (s, 3H), 3.55 (d, 1H), 2.90-2.70 (m, 6H), 1.45 (m, 9H), 1.35 (s, 9H).

Preparation 41: 1,2-Dipropylbenzene

1,1'-Bis(diphenylphosphino)ferrocenedichloro palladium(II) (0.35 g) is placed in a flask under an atmosphere of argon. The flask is cooled to 0° C and then propylzinc bromide (169.5 ml, 0.5 M in THF) is slowly added. 1,2-Dibromobenzene (5.00 g, 21.19 mmol), dissolved in THF (10 ml), is then slowly added and the reaction mixture stirred at 50° C. The reaction is shown to be complete by TLC after 24 hours and is quenched by the addition of 2M HCl (50 ml) and then 80-90% of the solvent is removed *in vacuo*. The residue is partitioned between ethyl acetate (250 ml) and water (250 ml). The organic layer is washed with water (250 ml) and brine (250 ml), dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to give the title

compound. ^{1}H nmr ($CDCl_3$, 400 MHz); 7.10 (m, 4H), 2.60 (m, 4H), 1.60 (m, 4H), 1.00 (m, 6H).

Preparation 42: Benzyl-[2-(3,4-dipropyl-phenyl)-ethyl]-amine hydrochloride

The title compound is prepared from 1,2-Dipropylbenzene using procedures analogous to those of Preparations 37, 33, 25 and 27. ^{1}H nmr (d_6-DMSO, 400 MHz); 9.40 (br s, 2H), 7.55 (m, 2H), 7.40 (m, 3H), 7.10 (d, 1H), 6.95 (m, 2H), 4.15 (m, 2H), 3.10 (m, 2H), 2.90 (m, 2H), 2.50 (m, 4H), 1.50 (m, 4H), 0.90 (m, 6H).

Preparation 43: (R)-1-(4-tert-Butoxy-2-isopropoxy-benzothiazol-7-yl)-2-(1,1dimethyl-2-phenyl-ethylamino)-ethanol

A solution of phentermine (0.728 g, 4.89 mmol) and N,O-bis(trimethylsilyl)acetamide (0.496 g, 2.44 mmol) in dry DMF (1 ml) is stirred at room temperature for 30 minutes. A solution of 4-tert.butoxy-2-isopropoxy-7-(R)-oxiranyl-benzothiazole (0.75 g, 2.44 mmol) in dry DMF (1 ml) is added and the reaction mixture is stirred at 80° C. The reaction is shown to be complete by TLC after 18 hours. The title compound is obtained after purification by flash column chromatography (silica, iso-hexane / ethyl acetate 1:1). MS (ES+) *m/e* 457 (MH^+).

Preparation 44: Benzyl-[2-(3-propyl-phenyl)-ethyl]-amine hydrochloride

The title compound is prepared from 3-Bromophenylacetic acid using procedures analogous to those of Preparations 25, 26 and 27. MS (ES+) *m/e* 254 (MH^+).

Preparation 45: Benzyl-[2-(3-butyl-phenyl)-ethyl]-amine hydrochloride

The title compound is prepared from 3-Bromophenylacetic acid using procedures analogous to those of Preparations 25, 26 and 27. MS (ES+) *m/e* 268 (MH^+).

Preparation 46: N-Benzyl-2-(4-hydroxy-phenyl)-acetamide

The title compound is prepared from 4-hydroxyphenylacetic acid using procedures analogous to that of Preparation 25 and purification by flash column chromatography (silica, iso-hexane / ethyl acetate 2:1). MS (ES+) *m/e* 242 (MH^+).

Preparation 47: N-Benzyl-2-(4-butoxy-phenyl)-acetamide

N-Benzyl-2-(4-hydroxy-phenyl)-acetamide(2.00 g, 8.25 mmol) is suspended in acetonitrile (30 ml). Caesium carbonate (5.40 g, 16.58 mmol), butyl bromide (1.07 ml, 9.95 mmol) and finally potassium iodide (0.41 g, 2.49 mmol) were added and the reaction mixture was refluxed. The

reaction was shown to be complete by HPLC after 16 hours. The reaction mixture is partitioned between ethyl acetate (100 ml) and water (100 ml). The organic layer is washed with water (150 ml) and brine (150 ml), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Recrystallisation from cyclohexane/ ethyl acetate gives the title compound. MS (ES+) *m/e* 298 (MH^+).

Preparation 48: Benzyl-[2-(4-butoxy-phenyl)-ethyl]-amine

Borane-THF complex (10 ml, 1M in THF) is added to N-Benzyl-2-(4-butoxy-phenyl)-acetamide 1.00 g, 3,36 mmol). The resulting slurry is stirred at room temperature. The reaction was shown to be complete by HPLC after 3 hours. Concentrated hydrochloric acid (5 ml) is slowly added to the ice-cooled reaction mixture and is then refluxed for 1.5 hours. The reaction mixture is cooled and treated with 4M NaOH until a basic solution is obtained. The reaction mixture is extracted with ethyl acetate and the organic layer is washed with water (150 ml) and brine (150 ml), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The title compound is obtained after purification by flash column chromatography (silica, iso-hexane / ethyl acetate 2:1). MS (ES+) *m/e* 284 (MH^+).

Preparation 49: Benzyl-[2-(3-butoxy-phenyl)-ethyl]-amine

The title compound is prepared from 3-hydroxyphenylacetic acid using procedures analogous to those of Preparations 46, 47 and 48. MS (ES+) *m/e* 284 (MH^+).

Preparation 50: Benzyl-[2-(3-pentyl-phenyl)-ethyl]-amine hydrochloride

The title compound is prepared from 3-Bromophenylacetic acid using procedures analogous to those of Preparations 25, 26 and 27. MS (ES+) *m/e* 282 (MH^+).

Preparation 51: (3-Bromo-phenyl)-acetic acid methyl ester

3-Bromophenylacetic acid (14.38g, 66.90mmol) is dissolved in methanol (100 ml). Concentrated sulfuric acid (2 ml) is added dropwise and the reaction mixture is stirred at room temperature for 18 hours. 80% of the solvent is removed *in vacuo* and the reaction mixture is partitioned between ethyl acetate (100 ml) and water (100 ml). The organic layer is washed with water (150 ml) and brine (150 ml), dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to give the title compound. ^1H nmr ($CDCl_3$, 400 MHz); 7.20 (m, 2H), 6.95 (m, 2H), 3.50 (s, 3H), 3.35 (s, 2H)

Preparation 52: 2-(3-Bromo-phenyl)-acetamide

(3-Bromo-phenyl)-acetic acid methyl ester (15.33 g, 66.90 mmol) is dissolved in methanol (50 ml) and ammonium hydroxide (100 ml). The reaction mixture is stirred at room temperature. The reaction is shown to be complete by TLC after 18 hours. The methanol is removed *in vacuo* and the product precipitates out. The solid is filtered off, washed with water and dried to give the title compd. MS (ES+) *m/e* 214 ($MH^+ - Br^{79}$), 216 ($MH^+ - Br^{81}$).

Preparation 53: 2-(3'-Methoxy-biphenyl-3-yl)-acetamide

2-(3-Bromo-phenyl)-acetamide (1.07 g, 5.00 mmol) is dissolved in THF (30 ml) and cooled to 0° C. 2-methoxyphenylboronic acid (0.76 g, 5.00 mmol) is added then sodium carbonate (1.06 g, 10.00 mmol) dissolved in water (24 ml). The reaction mixture is evacuated and charged with argon (3x). Tetrakis(triphenylphosphine)palladium (0.29 g, 0.25 mmol) is added and the reaction mixture is evacuated and charged with argon (3x). The reaction mixture is stirred at 80° C for 18 hours. The reaction mixture is extracted with ethyl acetate and the organic layer is washed with water (150 ml) and brine (150 ml), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The title compound is obtained after purification by flash column chromatography (silica, ethyl acetate). MS (ES+) *m/e* 242 (MH^+).

Preparation 54: 2-(3'-Methoxy-biphenyl-3-yl)-ethylamine hydrochloride

The title compound is prepared from 2-(3'-methoxy-biphenyl-3-yl)-acetamide using a procedure analogous to that of Preparation 48 and treatment with 1M HCl/Et_2O. ^1H nmr ($CDCl_3$, 400 MHz); 8.30 (br s, 3H), 7.40 (m, 2H), 7.30 (m, 1H), 7.20 (m, 1H), 7.10 (m, 2H), 7.05 (m, 1H), 6.75 (m, 1H), 3.75 (s, 3H), 3.05 (m, 2H), 2.95 (m, 2H).

Preparation 55: Benzyl-[2-(4-bromo-phenyl)-1-methyl-ethyl]-amine

4-bromophenylacetone (18.30 g, 85.91 mmol) and benzylamine (9.19 g, 85.91 mmol) are dissolved in ethanol (100 ml). 5%Pt-C (0.5 g) is added and the reaction mixture is stirred under an atmosphere of hydrogen. The reaction is shown to be complete by TLC after 18 hours. The catalyst is filtered off and the solvent is removed *in vacuo* to give the title compound. MS (ES+) *m/e* 304 ($MH^+ - Br^{79}$) and 306 ($MH^+ - Br^{81}$).

Preparation 56: Benzyl-[2-(4-bromo-phenyl)-1-methyl-ethyl]-carbamic acid benzyl ester

Benzyl-[2-(4-bromo-phenyl)-1-methyl-ethyl]-amine (17.00 g, 55.92 mmol) is dissolved in dichloromethane (250 ml). Triethylamine (6.21 g, 61.51 mmol) is added, then benzylchloroformate (10.49 g, 61.51 mmol), and the reaction mixture is stirred at room temperature. The reaction is shown to be complete by TLC after 18 hours. The reaction mixture is washed with

2M HCl, water and brine, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The title compound is obtained after purification by flash column chromatography (silica, iso-hexane / ethyl acetate 4:1). MS (ES+) *m/e* 438 ($MH^+ - Br^{79}$) and 440 ($MH^+ - Br^{81}$).

Preparation 57: Benzyl-[1-methyl-2-(4-propyl-phenyl)-ethyl]-carbamic acid benzyl ester

The title compound is prepared from benzyl-[2-(4-bromo-phenyl)-1-methyl-ethyl]-carbamic acid benzyl ester using a procedure analogous to that of Preparation 26 and purification by flash column chromatography (silica, iso-hexane / ethyl acetate 10:1). ^1H nmr ($CDCl_3$, 400 MHz); 7.40- 6.85(m, 16H), 5.10 (m, 2H), 4.50 (m, 1H), 4.20 (m, 1H), 2.90 (m, 1H), 2.65 (m, 1H), 2.50 (m, 2H), 1.60 (m, 2H), 1.10 (m, 3H), 0.90 (t, 3H)

Preparation 58: 1-Methyl-2-(4-propyl-phenyl)-ethylamine

Benzyl-[2-(4-propyl-phenyl)-1-methyl-ethyl]-carbamic acid benzyl ester (4.00 g, 9.13 mmol) is dissolved in methanol (100 ml) and the compound is deprotected by adding a catalytic amount of 10% palladium on charcoal and placing the solution under an atmosphere of H_2. The reaction is shown to be complete by TLC after 18 hours. The catalyst is filtered off and the solvent is removed *in vacuo* to give the title compound. MS (ES+) *m/e* 178 (MH^+).

Preparation 59: (R)-2-(4-Methoxy-phenyl)-1-methyl-ethylamine

The title compound is prepared by the procedure of R. Hett et al Organic Process Research & Development (1998), 2(2), 96-99.

Preparation 60: (S)-2-(4-Methoxy-phenyl)-1-methyl-ethylamine

The title compound is prepared by the procedure of R. Hett et al Organic Process Research & Development (1998), 2(2), 96-99.

Preparation 61: 1-(3-Butyl-phenyl)-3-chloro-propan-1-one

Butylbenzene (44.78 g, 334 mmol) and propionyl chloride (42.44 g, 334 mmol) are added dropwise to AlC13 (22.3 g, 167.8 mmol) in nitromethane (75 ml) over 1 hour. The reaction mixture is stirred at room temperature for 3 hours, after which 400 g of ice and 60 ml concentrated hydrochloric acid are added. The aqueous phase is extracted with ether, and the combined organic phases extracted with 2N HCI and saturated aqueous NaCl. The organic phase is dried over magnesium sulphate, filtered, and the solvent removed *in vacuo* to give the title compound. ^1H nmr ($CDCl_3$, 400 MHz); 7.85(d, 2H), 7.30(d, 2H), 3.90 (t, 2H), 3.40 (t, 2H), 2.65 (t, 2H), 1.60 (m, 2H), 1.35 (m, 2H), 0.90 (t, 3H).

Preparation 62: 6-Butyl-indan-1-one

1-(3-Butyl-phenyl)-3-chloro-propan-1-one (65.0 g, 290 mmol) is dissolved in concentrated sulphuric acid (250 ml) and heated to 90° C for 4 hours. The reaction mixture is cooled, ice (500 g) is added, and the aqueous solution extracted twice with toluene. The organic layer is washed with sodium bicarbonate, saturated aqueous NaCl, dried over magnesium sulphate. After filtration, the solvent is removed *in vacuo* to give the title compound.

Preparation 63: 6-Butyl-indan-1,2-dione 2-oxime

6-Butyl-indan-1-one (35.0 g, 186 mmol) is dissolved in methanol (250 ml) and brought up to 40° C. N-butyl nitrite (21.1 g, 205 mmol) is added dropwise, followed by the addition of concentrated HCI (5 ml). The reaction is shown to be complete by TLC after 1 hour. The reaction is brought to room temperature and the precipitate is filtered off, washed with ice-cold methanol and dried to give the title compound. ^{1}H nmr ($CDCl_3$, 400 MHz); 8.80 (br s, 1H), 7.80(d, 1H), 7.30(s, 1H), 7.25(d, 1H), 3.85 (s, 2H), 2.70 (t, 2H), 1.60 (m, 2H), 1.35 (m, 2H), 0.90 (t, 3H).

Preparation 64: 5-Butyl-indan-2-ylamine hydrochloride

6-Butyl-indan-1,2-dione 2-oxime (5.00 g, 23.04 mmol) is dissolved in acetic acid (75 ml) and concentrated sulfuric acid (5 ml). 10% Pd-C (1.00 g) is added and the reaction mixture is stirred under an atmosphere of hydrogen at 3 atmospheres. The reaction is shown to be complete by TLC after 18 hours. The catalyst is filtered off and the solution is made basic with 2M NaOH. The reaction mixture is extracted with ethyl acetate and the organic layer is washed with water and brine, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The residue is dissolved in Et_2O (100 ml) and treated with 1M HCl/ Et_2O (25 ml). The precipitate is filtered off and dried to give the title compound. ^{1}H nmr ($CDCl_3$, 400 MHz); 8.50 (br s, 3H), 7.05(m, 1H), 6.95(m, 2H), 4.00 (m, 1H), 3.25 (m, 2H), 3.10 (m, 2H), 2.50 (t, 2H), 1.50 (m, 2H), 1.25 (m, 2H), 0.80 (t, 3H).

Preparation 65: 2-(4-Amino-phenyl)-ethyl]-carbamic acid tert-butyl ester

The title compound is prepared from 4-(2-amino-ethyl)-phenylamine by the procedure of WO 01/42193. ^{1}H nmr ($CDCl_3$, 400 MHz); 6.95(d, 2H), 6.65(d, 2H), 4.50 (br s, 1H), 3.60 (s, 2H), 3.30 (m, 2H), 2.70 (m, 2H), 1.40 (s, 9H).

Preparation 66: [2-(4-Pyrrolidin-1-yl-phenyl)-ethyl]-carbamic acid tert-butyl ester

The title compound is prepared from [2-(4-Amino-phenyl)-ethyl]-carbamic acid tert-butyl ester by a procedure analogous to that of G. Verardo et al Synthesis (1999), No.1, 74-79. MS (ES+) *m/e* 291 (MH^+).

Preparation 67: 2-(4-Pyrrolidin-1-yl-phenyl)-ethylamine

The title compd is prepared from [2-(4-pyrrolidin-1-yl-phenyl)-ethyl]-carbamic acid tert-butyl ester by a procedure analogous to that of WO 01/42193. ^1H nmr ($CDCl_3$, 400 MHz); 7.10 (d, 2H), 6.55(d, 2H), 3.30 (m, 4H), 2.90 (t, 2H), 2.65 (t, 2H), 2.00 (m, 4H), 1.50 (s, 2H).

Preparation 68: 2-[4-(2-Amino-ethyl)-phenylamino]-1-phenyl-ethanol

The title compound is prepared by the procedure of WO 01/42193.

Preparation 69: Cis-Bicyclopentyl-2-ylamine and trans-Bicyclopentyl-2-ylamine

The title compounds are prepared from bicyclopentyl-2-one by procedures analogous to that of R. Hutchins et al J. Org. Chem. 1983, 48, 3412-3422.

Preparation 70: (1R,2R)-Bicyclopentyl-2-ylamine and (1S,2S)-Bicyclopentyl-2-ylamine

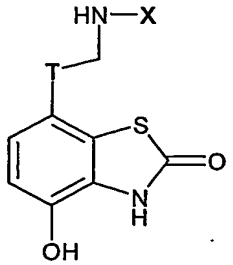
The title compounds are prepared from Bicyclopentyl-2-one by the procedures of S. Hartmann et al Eur. J. Med. Chem. 2000, 35, 377-392.

Preparation 71: Cis-2-Phenyl-cyclopentylamine

The title compound is prepared from 2-Phenyl-cyclopentanone by procedures analogous to that of R. Hutchins et al J. Org. Chem. 1983, 48, 3412-3422.

Examples 1 to 9

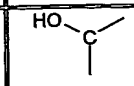
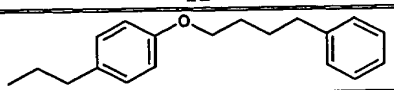
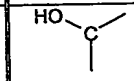
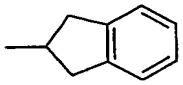
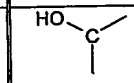
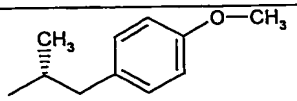
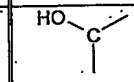
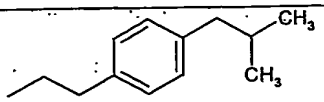
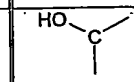
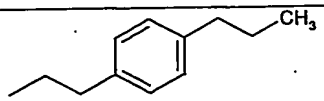
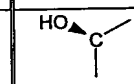
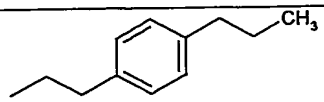
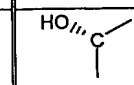
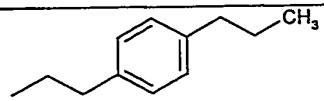
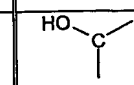
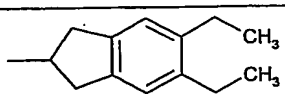
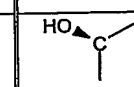
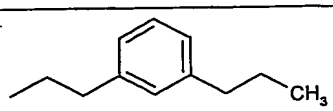
The following examples concern especially preferred compounds of formula I that are also compounds of formula XII



XII

wherein T and X are as shown in the following table, the method of preparation being described hereinafter. The table also shows characterising mass spectrometry data ([MH]+). The compounds of Examples 1 to 5 and 8 are prepared as free salts. The other compounds are made as hydrochloride salts.

TABLE 1

Ex.	T	X	MS [MH]+
1			479
2			343
3			375
4			387
5			373
6			373
7			373
8			399
9			373

Example 1: 4-hydroxy-7-(1-hydroxy-2-{2-[4-(4-phenyl-butoxy)-phenyl]-ethylamino}-ethyl)-3H-benzothiazol-2-one

Palladium black (0.2 g) is added portion-wise to a solution of 7-[2-(benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amino)-1-hydroxy-ethyl]-4-hydroxy-3H-benzothiazol-2-one (0.29 g) in formic acid (10 ml) at room temperature. After 1 hour the catalyst is removed by filtration and the filtrate partitioned between $CH_3CO_2CH_2CH_3$ and aqueous $NaHCO_3$. Evaporation of the $CH_3CO_2CH_2CH_3$ layers and recrystallisation from hexane / $CH_3CO_2CH_2CH_3$ gives the title compound. MS (ES+) 479.

Example 2: 4-hydroxy-7-[1-hydroxy-2-(indan-2-ylamino)-ethyl]-3H-benzothiazol-2-one

This compound is prepared from the product of Preparation 15 by a procedure analogous to that of Example 1. MS (ES+) 343.

Example 3: 4-hydroxy-7-{1-hydroxy-2-[(R)-2-(4-methoxy-phenyl)-1-methyl-ethylamino]-ethyl}-3H-benzothiazol-2-one

The title compound is prepared from 2-{benzyl-[(R)-2-(4-methoxy-phenyl)-1-methyl-ethyl]-amino}-N-methoxy-N-methyl-acetamide and (2-tert-butoxy-5-fluoro-phenyl)-thiocarbamic acid O-isopropyl by following procedures analogous to those of Preparations 10, 11 and 12 and Example 1. MS (ES+) 375.

Example 4: 4-hydroxy-7-{1-hydroxy-2-[2-(4-isobutyl-phenyl)-ethylamino]-ethyl}-3H-benzothiazol-2-one

The title compound is prepared from 2-{benzyl-[2-(4-isobutyl-phenyl)-ethyl]-amino}-N-methoxy-N-methyl-acetamide and (2-tert-butoxy-5-fluoro-phenyl)-thiocarbamic acid O-isopropyl ester by procedures analogous to those of Preparations 10, 11 and 12 and Example 1. MS (ES+) 387.

Example 5: 4-hydroxy-7-{1-hydroxy-2-[2-(4-propyl-phenyl)-ethylamino]-ethyl}-3H-benzothiazol-2-one

The title compound is prepared from 2-{benzyl-[2-(4-isobutyl-phenyl)-ethyl]-amino}-N-methoxy-N-methyl-acetamide and (2-tert-butoxy-5-fluoro-phenyl)-thiocarbamic acid O-isopropyl ester by procedures analogous to those of Preparations 10, 11 and 12 and Example 1. ^{1}H nmr (MeOH-d_4, 400 MHz); 7.16-6.97 (m, 4H), 6.86 (d, 1H, J = 8 Hz), 6.65 (d, 1H, J = 8 Hz), 4.87-4.85 (m, 1H), 3.20-3.12 (m, 2H), 3.10-3.02 (m, 2H), 2.89-2.87 (m, 2H), 2.49-2.44 (m, 2H), 1.57-1.46 (m, 2H), 0.84-0.79 (m, 3H).

Example 6: 4-hydroxy-7-{(R)-1-hydroxy-2-[2-(4-propyl-phenyl)-ethylamino]-ethyl}-3H-benzothiazol-2-one hydrochloride

Palladium black (5 g) is added portionwise to a solution of (R)-2-{benzyl-[2-(4-propyl-phenyl)-ethyl]-amino}-1-(4-tert-butoxy-2-isopropoxy-benzothiazol-7-yl)-ethanol (4.00 g in formic acid (25 ml) at room temperature. After 1 hour, filtration and evaporation gives the formate salt, which is dissolved in boiling ethyl acetate : MeOH (1 : 1), treated with decolourising charcoal and filtered hot. The solution is allowed to cool, 1 M HCl in Et_2O (10 ml) is added and the

solvent is removed *in vacuo*. The solid is triturated with ethyl acetate, filtered and dried. MS (ES+) *m/e* 373 (MH^+).

Example 7: 4-hydroxy-7-{(S)-1-hydroxy-2-[2-(4-propyl-phenyl)-ethylamino]-ethyl}-3H-benzothiazol-2-one hydrochloride

The title compound is prepared from (S)-1-(4-tert-butoxy-2-isopropoxy-benzothiazol-7-yl)-2-chloro-ethanol by procedures analogous to those of Preparations 30 and 31 and Example 6. MS (ES+) *m/e* 373 (MH^+).

Example 8: 7-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-4-hydroxy-3H-benzothiazol-2-one

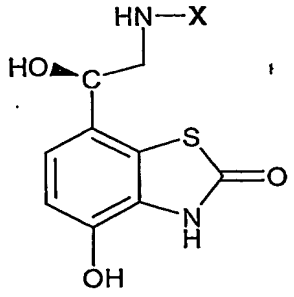
The title compound is prepared from 2-[benzyl-(5,6-diethyl-indan-2-yl)-amino]-N-methoxy-N-methyl-acetamide and (2-tert-butoxy-5-fluoro-phenyl)-thiocarbamic acid O-isopropyl ester by procedures analogous to those of Prep. 10, 11 and 12 and Example 1. MS (ES+) 399.

Example 9: 4-hydroxy-7-{(R)-1-hydroxy-2-[2-(3-propyl-phenyl)-ethylamino]-ethyl}-3H-benzothiazol-2-one hydrochloride

The title compd is prepared from (R)-2-{benzyl-[2-(3-propyl-phenyl)-ethyl]-amino}-1-(4-tert-butoxy-2-isopropoxy-benzothiazol-7-yl)-ethanol by a procedure analogous to that of Ex. 6.

Examples 10 to 47

The following examples concern especially preferred compounds of formula I that are also compounds of formula XIII

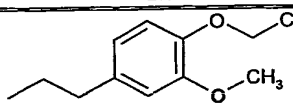
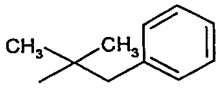
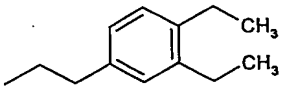
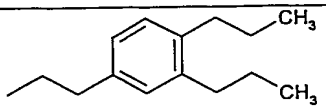
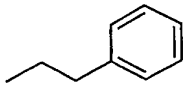
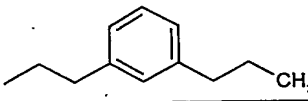
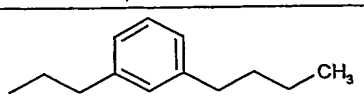
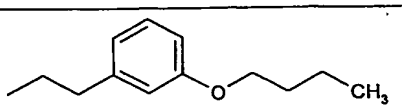
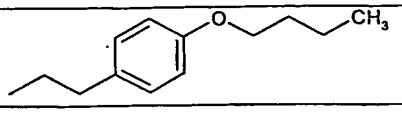
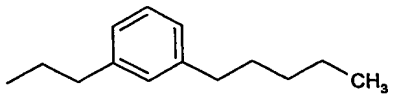


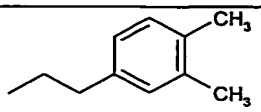
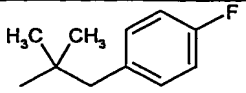
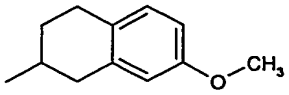
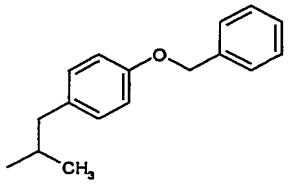
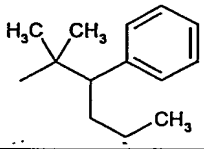
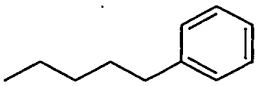
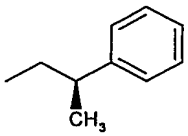
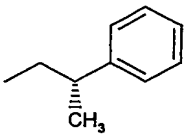
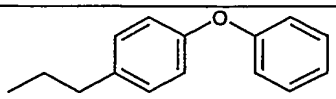
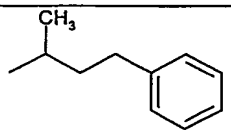
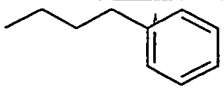
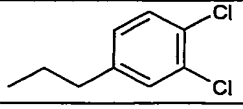
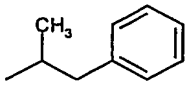
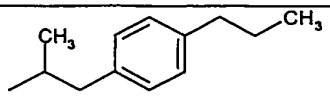
XIII

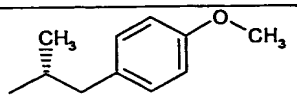
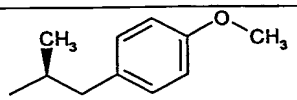
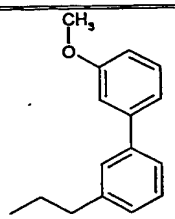
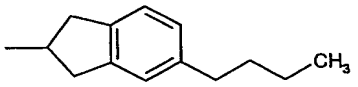
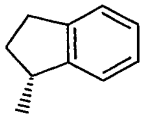
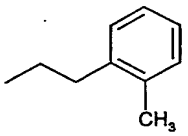
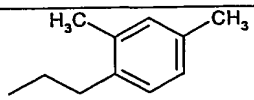
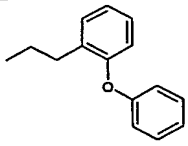
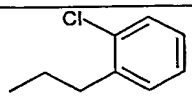
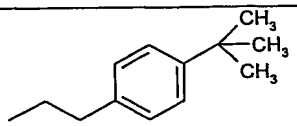
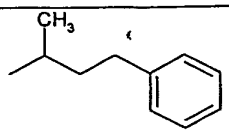
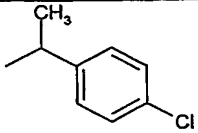
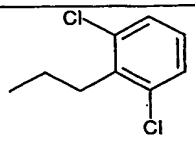
wherein X (of formula R^1-Ar-R^2) is as shown in the following table, the method of preparation being described hereinafter. The table also shows characterising mass spectrometry data ([MH]+). The compounds of Examples 12 and 16 to 18 are prepared as formate salts. The other compounds are made as trifluoroacetate salts. "Prep." refers to the number of one or

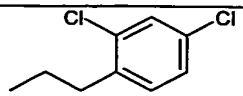
more of any Preparations of starting compounds detailed above that are used to prepare the compound of the Example. Compounds are analysed by high performance liquid chromatography (hplc) with mass spectral detection and "R. Time" represents the retention time for the compound with "MS" as the base peak from the mass spectra of the component eluting at that time point, from either a; CHROMOLITH RP18 SPEEDROD™ chromatographic column of dimensions 50 x 4.6 mm with the eluent system; A = 0.1% HCOOH in water, B = 0.1% HCOOH in acetonitrile, 5 to 95% B in 2.5 minutes at 3 ml/min at 25° C, or, where the reading is followed by an asterisk*, a CHROMOLITH RP18 SPEEDROD™ chromatographic column of dimensions 50 x 4.6 mm with the eluent system A = 0.1% TFA in water, B = 0.1% TFA in acetonitrile, 0 to 95% B in 2.5 minutes at 3 ml/min at 25° C.

TABLE 2

Ex.	X	Prep.	R. Time	MS [MH]+
10		39, 40	1.26	405.10
11		43	1.30	358.95
12		37, 38	1.45	387.05
13		41, 42	1.6	415.03
14		-	1.21	330.95
15		44	1.43	373.16
16		45	1.55	387.13
17		49	1.63	403.1
18		46, 47, 48	1.5	403.09
19		50	1.58	401.12

20		-	1.37	359.09
21		-	1.37	377.06
22		-	1.34	387.07
23		-	1.55	451.12
24		-	1.48	401.11
25		-	1.39	359.08
26		-	1.28	345.05
27		-	1.28	345.05
28		-	1.48	423.09
29		-	1.35	359.06
30		-	1.32	345.05
31		-	1.44	398.99
32		-	1.3	345.02
33		55, 56, 57, 58	1.53	387.08

34		59	1.32	375.76
35		60	1.3	375.76
36		51, 52, 53, 54	1.48	437.87
37		61, 62, 63, 64	1.55	398.9
38		-	1.22*	342.86
39		-	1.29*	344.87
40		-	1.41*	358.99
41		-	1.47*	422.96
42		-	1.52*	364.96
43		-	1.73*	387.07
44		-	1.52*	359.01
45		-	1.5*	364.97
46		-	1.52*	400.94 (50%)

47		-	1.6*	400.93 (25%)

Example 10: 7-{(R)-2-[2-(4-Ethoxy-3-methoxy-phenyl)-ethylamino]-1-hydroxy-ethyl}-4-hydroxy-3H-benzothiazol-2-one trifluoroacetate

Palladium black (0.4 g) is added portion-wise to a solution of (R)-2-{Benzyl-[2-(4-ethoxy-3-methoxy-phenyl)-ethyl]-amino}-1-(4-tert-butoxy-2-isopropoxy-benzothiazol-7-yl)-ethanol (0.45 g) in formic acid (5 ml) at room temperature. After 24 hours the catalyst is removed by filtration. Evaporation of the formic acid and purification by reverse phase chromatography (ISOLUTE FLASH C18, 0-50% methylcyanide in water (0.1% TFA)) gives the title compound. MS (ES+) *m/e* 405 (MH^+).

Example 11: 7-[(R)-2-(1,1-Dimethyl-2-phenyl-ethylamino)-1-hydroxy-ethyl]-4-hydroxy-3H-benzothiazol-2-one

A solution of (R)-1-(4-tert-Butoxy-2-isopropoxy-benzothiazol-7-yl)-2-(1,1dimethyl-2-phenyl-ethylamino)-ethanol in formic acid (10 ml) is stirred at room temperature. The reaction is shown to be complete by LCMS after 48 hours. Evaporation of the formic acid and purification by reverse phase chromatography (ISOLUTE FLASH C18, 0-50% methylcyanide in water (0.1% TFA)) gives the title compound. MS (ES+) *m/e* 359 (MH^+).

Example 12: 7-{(R)-2-[2-(3,4-Diethyl-phenyl)-ethylamino]-1-hydroxy-ethyl}-4-hydroxy-3H-benzothiazol-2-one

Palladium black (0.4 g) is added portion-wise to a solution of (R)-2-{2-(3,4-Diethyl-phenyl)-ethylamino]-1-hydroxy-ethyl]-amino}-1-(4-tert-butoxy-2-isopropoxy-benzothiazol-7-yl)-ethanol (prepared from the product of Preparation 38 following a procedure analogous to that of Préparation 31) (0.40 g) in formic acid (5 ml) at room temperature. After 24 hours the catalyst is removed by filtration. Evaporation of the formic acid and purification by reverse phase chromatography (ISOLUTE FLASH C18, 0-50% methylcyanide in water (0.1% formic acid)) gives the title compound. MS (ES+) *m/e* 387.05 (MH^+).

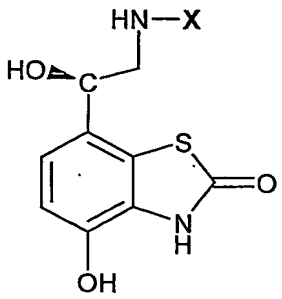
The compounds of Examples 13, 15, 19 and 32 are made using procedures that are analogous to that used in Example 10.

The compounds of Examples 14, 20 to 31 and 33 to 47 are made using procedures that are analogous to that used in Example 11.

The compounds of Examples 16 to 18 are made using procedures that are analogous to that used in Example 12.

Examples 48 to 131

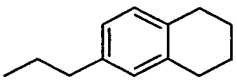
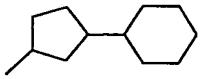
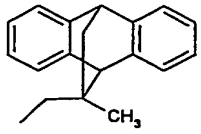
The following examples concern especially preferred compounds of formula I that are also compounds of formula XIII

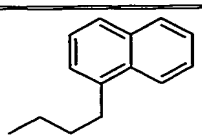
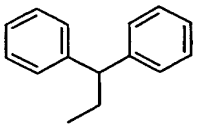
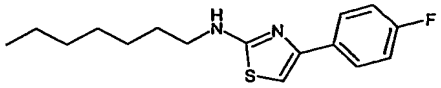
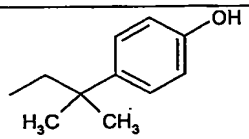
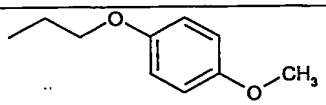
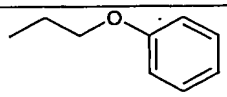
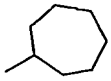
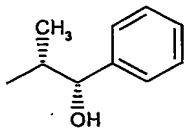
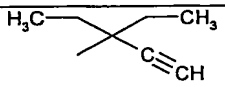
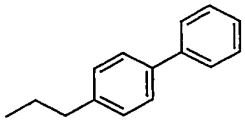
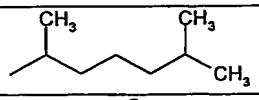
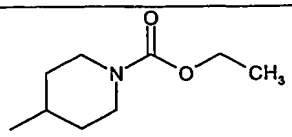
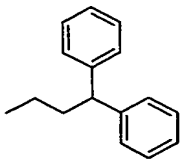
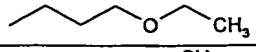
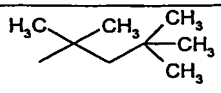


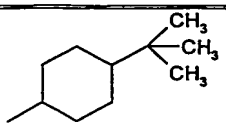
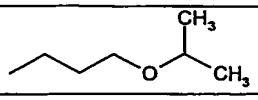
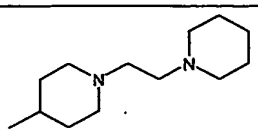
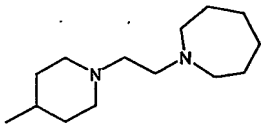
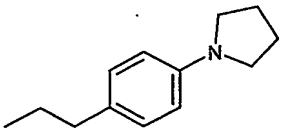
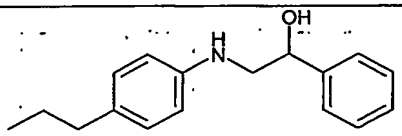
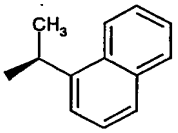
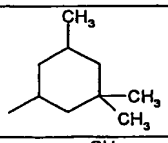
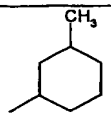
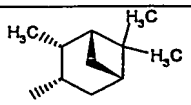
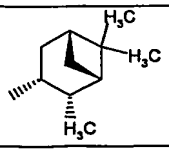
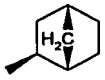
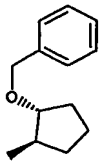
XIII

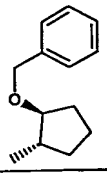
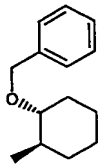
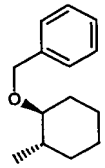
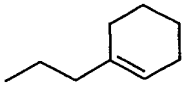
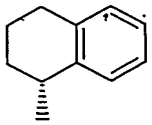
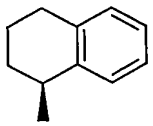
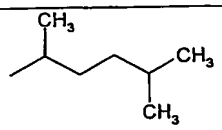
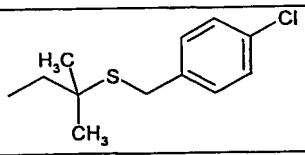
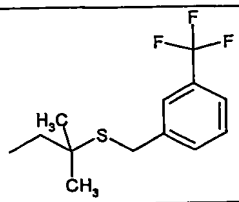
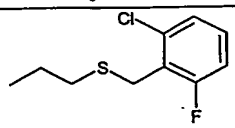
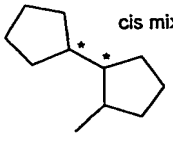
wherein X ((of formula R^1-Ar-R^2 or R^a-Y) is as shown in the following table, the method of preparation being described hereinafter. The table also shows characterising mass spectrometry data ([MH]+). The compounds of all of these Examples are prepared as trifluoroacetate salts. "Prep." refers to the number of one or more of any Preparations of starting compounds detailed above that are used to prepare the compound of the Example. Compounds are analysed by high performance liquid chromatography (hplc) with mass spectral detection and "R. Time" represents the retention time for the compound with "MS" as the base peak from the mass spectra of the component eluting at that time point, from either a; CHROMOLITH RP18 SPEEDROD™ chromatographic column of dimensions 50 x 4.6 mm with the eluent system; A = 0.1% HCOOH in water, B = 0.1% HCOOH in acetonitrile, 5 to 95% B in 2.5 minutes at 3 ml/min at 25° C, or, where the reading is followed by an asterisk*, a CHROMOLITH RP18 SPEEDROD™ chromatographic column of dimensions 50 x 4.6 mm with the eluent system A = 0.1% TFA in water, B = 0.1% TFA in acetonitrile, 0 to 95% B in 2.5 minutes at 3 ml/min at 25° C.

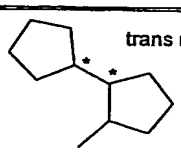
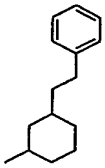
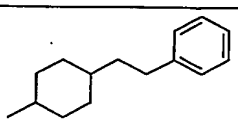
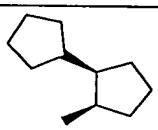
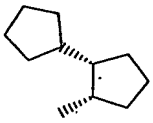
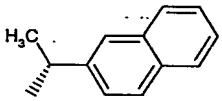
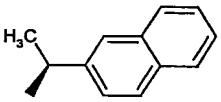
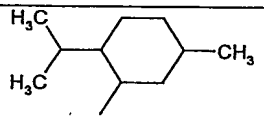
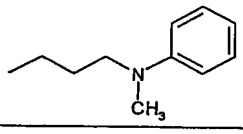
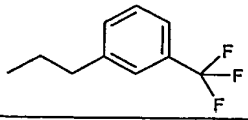
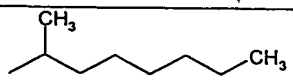
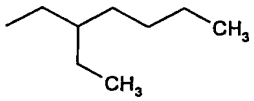
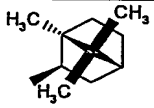
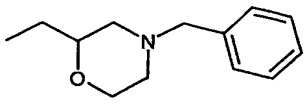
TABLE 3

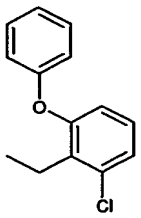
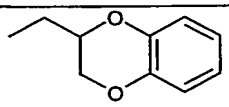
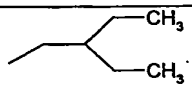
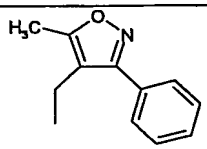
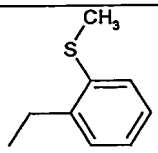
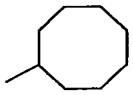
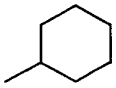
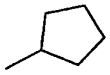
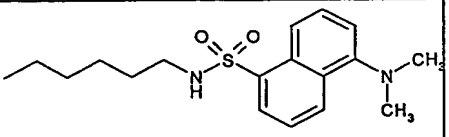
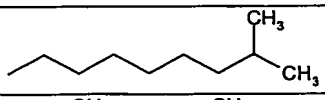
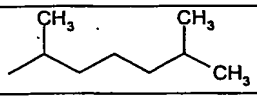
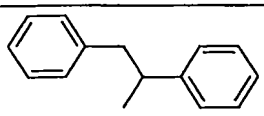
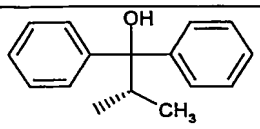
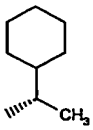
Ex.	X	Prep.	R. Time	MS [MH]+
48		33, 34, 35, 36	1.44	385
49		-	1.47	377.12
50		-	1.52	459.12

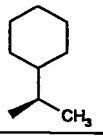
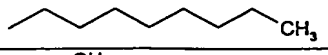
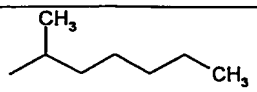
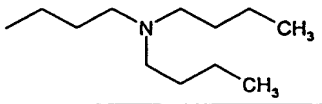
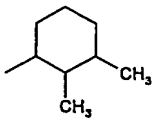
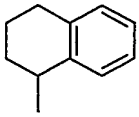
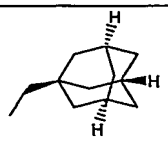
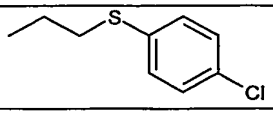
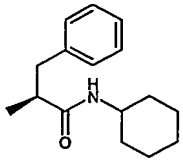
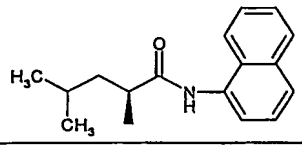
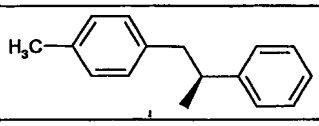
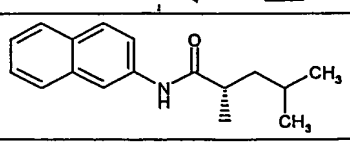
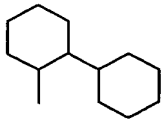
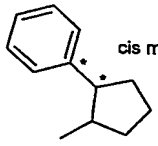
51		-	1.47	395.09
52		-	1.44	407.08
53		-	1.41	503.13
54		-	1.2	375.07
55		-	1.25	377.06
56		-	1.24	347.04
57		-	1.25	323.05
58		-	1.25	361.06
59		-	1.25	321.06
60		-	1.5	407.09
61		-	1.42	339.09
62		-	1.16	382.07
63		-	1.5	421.1
64		-	1.17*	312.99
65		-	1.47*	339.04

66		-	1.61*	365.04
67		-	1.26*	326.99
68		-	0.17	420.96
69		-	0.18	434.96
70		65, 66, 67	1.25	399.9
71		68	1.3	465.01
72		-	1.33*	380.86
73		-	1.6*	351.04
74		-	1.45*	323.01
75		-	1.62*	363.02
76		-	1.62*	363.03
77		-	1.41*	320.98
78		-	1.55*	401.01

79		-	1.54*	401.01
80		-	1.62*	415.02
81		-	1.61*	415.01
82		-	1.36*	334.99
83		-	1.3*	356.99
84		-	1.31*	356.99
85		-	1.33*	324.99
86		-	1.49*	438.93
87		-	1.53*	472.94
88		-	1.41*	428.89
89	 cis mixture	69	1.42	363.02

90		69	1.43	363.01
91		-	1.55	413.03
92		-	1.56	413.02
93		70	1.42	393.01
94		70	1.43	363.02
95		-	1.57*	381.01
96		-	1.57*	381.01
97		-	1.67*	365.07
98		-	1.28*	374.04
99		-	1.63*	398.99
100		-	1.65*	339.06
101		-	1.64*	339.06
102		-	1.59*	363.06
103		-	1.29*	416.06

104		-	1.65*	442.98
105		-	1.47*	374.99 (80%)
106		-	1.46*	311.03
107		-	1.46*	398.01
108		-	1.46*	362.97
109		-	1.53*	337.05
110		-	1.39*	309.01
111		-	1.32*	295
112		-	1.45*	545.1
113		-	1.67*	353.06
114		-	1.6*	339.04
115		-	1.61*	407.02
116		-	1.57*	437.02
117		-	1.5*	337.02

118		-	1.5*	337.03
119		-	1.67*	339.05
120		-	1.53*	325.03
121		-	1.35*	396.1
122		-	1.5*	337.03
123		-	1.47*	357.02
124		-	1.6*	375.05
125		-	1.59*	396.94
126		-	1.63*	456.08
127		-	1.65*	466.09
128		-	1.67*	421.04
129		-	1.71*	466.07
130		-	1.7*	391.08
131	 cis mixture	71	1.21	371

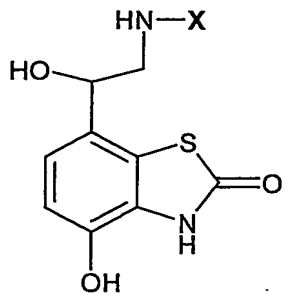
Example 48: 4-Hydroxy-7-{(R)-1-hydroxy-2-[2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-ethylamino]-ethyl}-3H-benzothiazol-2-one formate

Palladium black (0.4 g) is added portion-wise to a solution of (R)-2-{benzyl-[2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-ethyl]-amino}-1-(4-tert-butoxy-2-isopropoxy-benzothiazol-7-yl)-ethanol (0.40 g) in formic acid (5 ml) at room temperature. After 24 hours the catalyst is removed by filtration. Evaporation of the formic acid and purification by reverse phase chromatography (ISOLUTE FLASH C18, 0-50% methylcyanide in water (0.1% formic acid)) gives the title compound. MS (ES+) *m/e* 385 (MH^+).

The compounds of Examples 51 to 131 are made using procedures that are analogous to that used in Example 11.

CLAIMS

1. A compound of formula I



I

in free or salt or solvate form, wherein

X is $-R^1-Ar-R^2$ or $-R^a-Y$;

Ar denotes a phenylene group optionally substituted by halo, hydroxy, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy, C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl, phenyl, C_1-C_{10}-alkyl substituted by phenyl, C_1-C_{10}-alkoxy substituted by phenyl, C_1-C_{10}-alkyl-substituted phenyl or by C_1-C_{10}-alkoxy-substituted phenyl;

R^1 and R^2 are attached to adjacent carbon atoms in Ar, and
either R^1 is C_1-C_{10}-alkylene and R^2 is hydrogen, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy or halogen
or R^1 and R^2 together with the carbon atoms in Ar to which they are attached denote a 5-, 6- or 7-membered cycloaliphatic ring;

R^a is a bond or C_1-C_{10}-alkylene optionally substituted by hydroxy, C_1-C_{10}-alkoxy, C_6-C_{10}-aryl or C_7-C_{14}-aralkyl; and

Y is C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy, C_2-C_{10}-alkenyl or C_2-C_{10}-alkynyl optionally substituted by halo, cyano, hydroxy, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy or halo-C_1-C_{10}-alkyl;
C_3-C_{10}-cycloalkyl optionally fused to one or more benzene rings and optionally substituted by C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy, C_3-C_{10}-cycloalkyl, C_7-C_{14}-aralkyl, C_7-C_{14}-aralkyloxy or C_6-C_{10}-aryl optionally substituted by halo, hydroxy, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy or halo-C_1-C_{10}-alkyl;

C_6-C_{10}-aryl optionally substituted by halo, hydroxy, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy, C_1-C_{10}-haloalkyl, phenoxy, C_1-C_{10}-alkylthio, C_6-C_{10}-aryl, 4- to 10- membered heterocyclic ring having at least one ring nitrogen, oxygen or sulphur atom, or by NR^bR^c where R^b and R^c are each independently C_1-C_{10}-alkyl optionally substituted by hydroxy, C_1-C_{10}-alkoxy or phenyl or R^b may additionally be hydrogen;

phenoxy optionally substituted by C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy or by phenyl optionally substituted by C_1-C_{10}-alkyl or C_1-C_{10}-alkoxy;

a 4- to 10-membered heterocyclic ring having at least one ring nitrogen, oxygen or sulphur atom, said heterocyclic ring being optionally substituted by halo, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy, halo-C_1-C_{10}-alkyl, C_6-C_{10}-aryl, C_7-C_{14}-aralkyl, C_7-C_{14}-aralkyloxy, C_1-C_{10}-alkoxycarbonyl or a 4- to 10-membered heterocyclyl-C_1-C_{10}-alkyl;

$-NR^dR^e$ where R^d is hydrogen or C_1-C_{10}-alkyl and R^e is C_1-C_{10}-alkyl optionally substituted by hydroxy, or R^e is C_6-C_{10}-aryl optionally substituted by halo, or R^e is a 4- to 10-membered heterocyclic ring having at least one ring nitrogen, oxygen or sulphur atom which ring is optionally substituted by phenyl or halo-substituted phenyl or R^e is C_6-C_{10}-arylsulfonyl optionally substituted by C_1-C_{10}-alkylamino or di(C_1-C_{10}-alkyl)-amino;

$-SR^f$ where R^f is C_6-C_{10}-aryl or C_7-C_{14}-aralkyl optionally substituted by halo, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy or C_1-C_{10}-haloalkyl; or

$-CONHR^g$ where R^g is C_1-C_{10}-alkyl, C_3-C_{10}-cycloalkyl or C_6-C_{10}-aryl.

2. A compound according to claim 1, in which
X is $-R^1$-Ar-R^2 or $-R^a$-Y;
Ar denotes a phenylene group optionally substituted by halo, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy or by C_1-C_{10}-alkoxy substituted by phenyl;
R^1 and R^2 are attached to adjacent carbon atoms in Ar; and
either R^1 is C_1-C_{10}-alkylene and R^2 is hydrogen,
or R^1 and R^2 together with the carbon atoms in Ar to which they are attached denote a 5-, 6- or 7-membered cycloaliphatic ring;

R^a is a bond or C_1-C_{10}-alkylene optionally substituted by hydroxy, C_6-C_{10}-aryl or C_7-C_{14}-aralkyl; and

Y is C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy or C_2-C_{10}-alkynyl; C_3-C_{10}-cycloalkyl optionally fused to one or more benzene rings and optionally substituted by C_1-C_{10}-alkyl, C_3-C_{10}-cycloalkyl, C_7-C_{14}-aralkyl, C_7-C_{14}-aralkyloxy or C_6-C_{10}-aryl; C_6-C_{10}-aryl optionally substituted by halo, hydroxy, C_1-C_{10}-alkyl, phenoxy, C_1-C_{10}-alkylthio, C_6-C_{10}-aryl, a 4- to 10-membered heterocyclic ring having at least one ring nitrogen atom, or by NR^bR^c where R^b and R^c are each independently C_1-C_{10}-alkyl optionally substituted by hydroxy or phenyl or R^b may additionally be hydrogen; phenoxy optionally substituted by C_1-C_{10}-alkoxy; a 4- to 10-membered heterocyclic ring having at least one ring nitrogen or oxygen atom, said heterocyclic ring being optionally substituted by C_1-C_{10}-alkyl, C_6-C_{10}-aryl, C_7-C_{14}-aralkyl, C_1-C_{10}-alkoxycarbonyl or by a 4- to 10-membered heterocyclyl-C_1-C_{10}-alkyl; $-NR^dR^e$ where R^d is hydrogen or C_1-C_{10}-alkyl and R^e is C_1-C_{10}-alkyl, or R^e is a 4- to 10-membered heterocyclic ring having at least one ring nitrogen or oxygen atom which ring is optionally substituted by halo-substituted phenyl or R^e is C_6-C_{10}-arylsulfonyl optionally substituted by di(C_1-C_{10}-alkyl)amino; $-SR^f$ where R^f is C_6-C_{10}-aryl or C_7-C_{14}-aralkyl optionally substituted by halo or C_1-C_{10}-haloalkyl; or $-CONHR^g$ where R^g is C_3-C_{10}-cycloalkyl or C_6-C_{10}-aryl.

3. A compound according to claim 2, in which

X is $-R^1$-Ar-R^2 or R^a-Y;

Ar denotes a phenylene group optionally substituted by halo, C_1-C_4-alkyl, C_1-C_4-alkoxy or by C_1-C_4-alkoxy substituted by phenyl;

R^1 and R^2 are attached to adjacent carbon atoms in Ar, and

either R^1 is C_1-C_4-alkylene and R^2 is hydrogen,

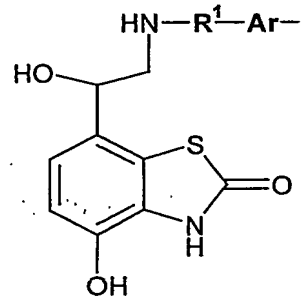
or R^1 and R^2 together with the carbon atoms in Ar to which they are attached denote a 5-, 6- or 7-membered cycloaliphatic ring, especially a 5-membered cycloaliphatic ring;

R^a is a bond or C_1-C_4-alkylene optionally substituted by hydroxy, C_6-C_8-aryl or C_7-C_{10}-aralkyl; and

Y is C_1-C_4-alkyl, C_1-C_4-alkoxy or C_2-C_4-alkynyl; C_3-C_6-cycloalkyl optionally fused to one or more benzene rings and optionally substituted by C_1-C_4-alkyl, C_3-C_6-cycloalkyl, C_7-C_{10}-aralkyl, C_7-C_{10}-aralkyloxy or C_6-C_8-aryl; C_6-C_8-aryl optionally substituted by halo, hydroxy, C_1-C_4-alkyl, phenoxy, C_1-C_4-alkylthio, C_6-C_8-aryl, a 4- to 8-membered heterocyclic ring having at least one ring nitrogen atom, or by NR^bR^c where R^b and R^c are each independently C_1-C_4-alkyl optionally substituted by hydroxy or phenyl or R^b may additionally be hydrogen; phenoxy optionally substituted by C_1-C_4-alkoxy; a 4- to 8-membered heterocyclic ring having

at least one ring nitrogen or oxygen atom, said heterocyclic ring being optionally substituted by C_1-C_4-alkyl, C_6-C_8-aryl, C_7-C_{10}-aralkyl, C_1-C_4-alkoxycarbonyl or by a 4- to 8-membered heterocyclyl-C_1-C_4-alkyl; -NR^dR^e where R^d is hydrogen or C_1-C_4-alkyl and R^e is C_1-C_4-alkyl, or R^e is a 4- to 8-membered heterocyclic ring having at least one ring nitrogen or sulphur atom which ring is optionally substituted by halo-substituted phenyl or R^e is C_6-C_8-arylsulfonyl optionally substituted by di(C_1-C_4-alkyl)amino; -SR^f where R^f is C_6-C_8-aryl or C_7-C_{10}-aralkyl optionally substituted by halo or C_1-C_4-haloalkyl; or -$CONHR^g$ where R^g is C_3-C_6-cycloalkyl or C_6-C_8-aryl.

4. A compound according to claim 1 that is also a compound of formula II



II

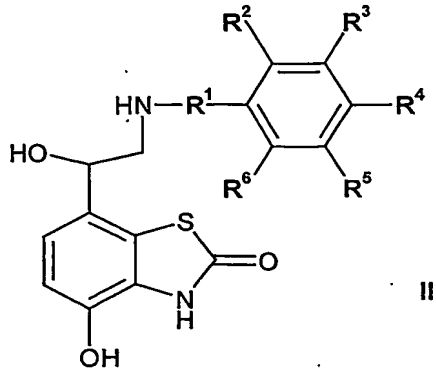
in free or salt or solvate form, where

Ar denotes a phenylene group optionally substituted by one or more substituents selected from halogen, C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, or C_1-C_8-alkoxy substituted by phenyl, C_1-C_8-alkyl-substituted phenyl or by C_1-C_8-alkoxy-substituted phenyl,

R^1 and R^2 are attached to adjacent carbon atoms in Ar, and

either R^1 is C_1-C_8-alkylene and R^2 is hydrogen, C_1-C_8-alkyl, C_1-C_8-alkoxy or halogen or R^1 and R^2 together with the carbon atoms in Ar to which they are attached denote a 5-, 6- or 7-membered cycloaliphatic ring.

5. A compound according to claim 1 that is also a compound of formula III



III

in free or salt or solvate form, where R^1 is C_2-C_4-alkylene and R^2 is hydrogen, or R^1 and R^2 together with the carbon atoms to which they are attached on the indicated benzene ring denote a 5-membered cycloaliphatic ring, R^3 and R^6 are each hydrogen, R^4 is hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy or C_1-C_4-alkoxy substituted by phenyl and R^5 is hydrogen or C_1-C_4-alkyl.

6. A compound of formula I as defined in claim 1, substantially as described in any one of the foregoing Examples.

7. A compound according to any preceding claim for use as a pharmaceutical.

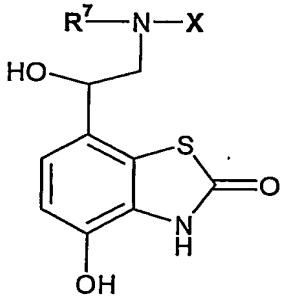
8. A pharmaceutical composition comprising as active ingredient a compound according to any one of claims 1 to 6, optionally together with a pharmaceutically acceptable diluent or carrier therefor.

9. Use of a compound according to any one of claims 1 to 6 for the manufacture of a medicament for the treatment of a condition which is prevented or alleviated by activation of the β_2-adrenoreceptor.

10. Use of a compound according to any one of claims 1 to 6 for the manufacture of a medicament for the treatment of an obstructive or inflammatory airways disease.

11 A process for the preparation of a compound of formula I in free or salt or solvate form which comprises

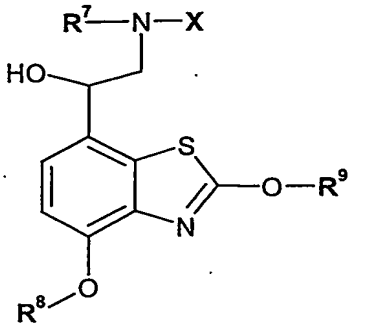
(i) either (A) reacting a compound of formula IV



IV

where X is as hereinbefore defined and R^7 denotes a protecting group, to replace R^7 by hydrogen,

or (B) reacting a compound of formula V



V

where X and R^7 are as hereinbefore defined and R^8 and R^9 each independently denote a protecting group, to convert groups R^7, R^8 and R^9 to hydrogen; and

(ii) recovering the compound of formula I in free or salt or solvate form.